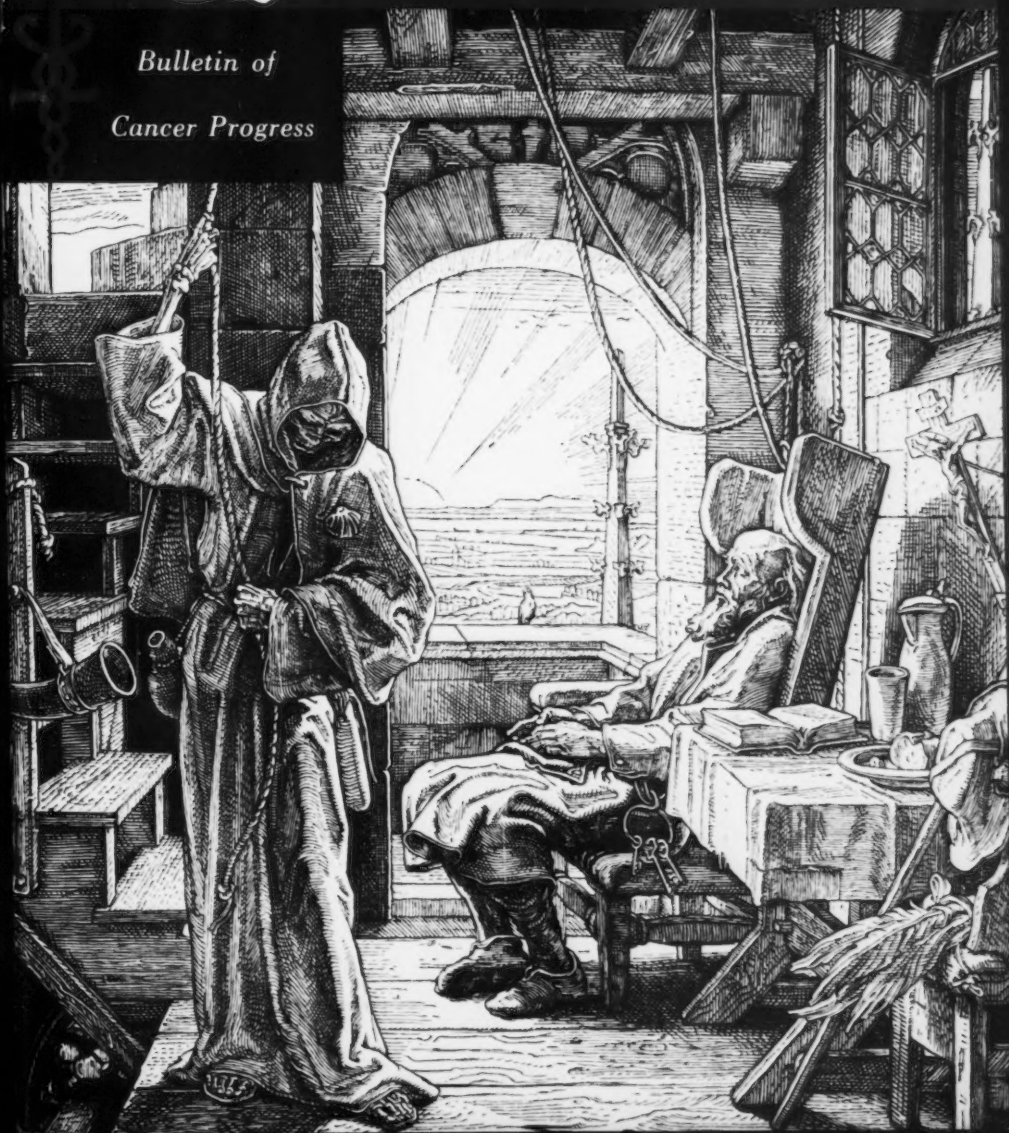


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*Ca*

*Bulletin of  
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*"let me go  
quietly"*

Criteria of incurability of cancer are still vague and variable. When widespread extension and metastases have developed, the family doctor is often justifiably more apt to despair of cure than are the surgeon and radiologist.

Before hope for cure is abandoned, each patient should be given group study. When it is agreed that curative surgery or radiation would be unavailing, palliative treatment is given—surgery, radiation, chemotherapy and endocrine therapy.

Usually it is the general practitioner who accepts responsibility for the management and comfort of the incurable patient. He consults with the surgeon and the radiologist concerning possible palliative procedures. He applies his art and science in relieving pain, insomnia, and gastrointestinal, nutritional and psychological symptoms.

In the terminal stage his experience and judgment tell him when to turn his attention from extending life for a few hours toward easing the hopeless patient's last moments. This the patient's family appreciates more than undue protraction of the dying process by use of the modern methods of scientific medicine—"doing everything that can be done."

After George Washington, dying of edema of the larynx, had suffered repeated bleedings, purgings and blisterings—then current methods of scientific medicine, he implored his persecutors: "I pray you to take no more trouble for me. Let me go quietly."

Cover—*Death the Friend* by Alfred Rethel (1816-1859). Bettmann Archive.

The abstract concept of Death as a person with absolute power was unknown in the early Christian era, and first appeared in the middle ages. This personalized idea of Death was not unknown to the ancients, and was probably revived by the religious pantomimes, processions and dances in which, Death, impersonated, played a dominant role as a friend, a judge, or an avenger (*Danse Macabre*). The idea of the Dance of Death appeared in the 13th century, first in literature and then in painting and sculpture. Many examples adorned church and monastery walls, especially after the plague in the 14th century. This woodcut is from the key picture of Rethel's magnificent series of the Dance of Death. It portrays quiet resignation and peace in contrast to the horror scenes of the others in the series. On the right is the old man, marked for death. To him, as to the properly managed terminal cancer patient, Death is no horrible specter. His hands are at final rest after he has laid aside his book of active life. The crucifix and the pilgrim hat speak eloquently of his cruel but God-given lifetime. The last rays of the setting sun are symbolic

of the perishability of all earthly things. On the other side of the picture is Death—dignified and quiet, with grieved expression and bent to the task of pulling the bell rope signalling the flight of another soul; an artistic synthesis of the theme "Death the Liberator".

*Suns may rise and sink again  
But for us, when our brief light goes out  
There is one long night for sleeping.*

—Catullus, *Lines to Lesbia*



# NEWSLETTER

MAY-JUNE, 1959

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Shimkin (NCI) recently announced plans for international cooperation in assembling essential data concerning a million cancer patients in England, Denmark, Finland, France, Norway and this country. Already some 200 hospitals in the United States are submitting data on diagnosis, therapy, pathology and survival of cancer patients to the End Results Evaluation Program of the National Cancer Institute. At the 8th International Cancer Congress in Moscow in 1962 plans for a comprehensive International Cancer Registry will be presented.

Murray (U. of Toronto) injected malignant tumor cells from patients in the operating room into horses. He used serum from these horses to treat terminal patients with cancer of the breast, stomach and colon. Injection of 300 ml. of the serum prolonged life in many patients and nearly always gave complete control of pain. Of 131 patients with breast cancer, 10 are living three years after treatment, as are 10 of 30 patients with cancer of the stomach and several of 20 with cancer of the colon.

Clemmesen (Copenhagen) reports that in Denmark the incidence rate of lung cancer is 50 per 100,000 -- 10 times its rate 20 years ago, and that the more tobacco consumed, the more lung cancer. In the United States the incidence of lung cancer does not follow the curve of tobacco consumption, probably because Americans do not smoke their cigarettes to such short butts. The increasing incidence of bladder papilloma parallels that of lung cancer and is also statistically related to cigarette smoking.

Hammack (U. of Alabama), using electrophoresis, the ultracentrifuge and gel diffusion studies, found that the abnormal blood proteins of myeloma and of plasma cell leukemia are similar, and that in one case of myeloma with the characteristic protein, plasma cell leukemia did not appear for three years. He reasons, therefore, that these two conditions -- myeloma and plasma cell leukemia -- are late manifestations of another single disease. He reported three other cases with abnormal myeloma protein that have not yet developed plasma cell leukemia, but are expected to do so.

The presence of abnormal blood proteins, therefore, can be used to predict the onset of leukemia, making earlier diagnosis possible.

Sinsheimer (Cal. Tech.) has discovered in a dwarf virus a desoxyribonucleic acid (DNA) with but a single strand of linked nucleotides instead of the double strand as in all other DNAs analyzed to date. The dwarf virus, which infects and destroys sewage bacteria, contains only a single molecule of DNA; other viruses have as many as ten. This virus has twelve sides instead of being round, rod-shaped or any of the other conventional virus forms. Discovery of this one-strand DNA casts some doubt on the conventionally accepted mechanism of cell division in regard to DNA and necessitates reconsideration of several basic biochemical concepts.

Baruah (Assam Medical College) studied the cytologic response to transplanted tumors in rats during growth and regression. Lymph nodes of normal rats contain few plasma cells, but during tumor growth they increase in weight and the medullary cords contain greatly increased numbers of plasma cells. These plasma cells take part in tumor antibody production, and their reactions in tissues correspond to immunologic changes in the host. Living tumor cells are essential to this plasma cell response. During inhibition and regression of the tumor a local response of great numbers of plasma cells around the tumor occurs. The presence of a circulating antibody is considered to be probable.

Heller (NCI) announced that \$23,000,000 a year is being expended to develop a nation-wide chemotherapy screening program, which includes searching for possible anticancer drugs, screening them for activity against animal tumors, selecting of the most promising for toxicity tests and trial in higher animals, and, finally, clinical testing in studies in 150 hospitals with 3,000 available patients. Among the thousands of compounds screened are three that have recently reached the stage of clinical testing -- 5-fluorouracil, 5-fluorodeoxyuridine and 6-azauracil.

A recent monograph by Dorn and Cutler of NCI on Morbidity of Cancer in the United States relates the incidence of cancer of certain sites with socioeconomic status. Cancer of the breast is more frequent in patients in higher income brackets. Cancers of the prostate, kidney, tongue and vagina have little or no economic correlation. Incidence of cancer

(Continued after page 108)



### Progress

New York, N. Y.

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## a glance . . .

**one-minute abstracts  
of the literature  
on palliation of cancer . . .**

### **Management of Advanced Cancer**

The advanced case of cancer is defined as one which by reason of distant metastases or of extensive local spread cannot be dealt with by the routine and classical operations or by other conventional methods. Many such patients, considered doomed to early death, make surprising progress, often enjoying useful and rewarding lives, when skillful management is allied to a high resistance to the disease. The dread of death is not concerned with physical pain or distress so much as with the fear and dread of leaving the world. A last illness may be long and painful, but the closing moments of life are, as a rule, free from suffering, as death is quite commonly preceded by total unconsciousness. The "agony of death" concerns the watcher at the bedside rather than the subject of pity. The following topics are discussed in their relation to the advanced cancer patient: extended and palliative surgery, radiotherapy, hormones and surgery of the endocrine glands in hormone dependent tumors, chemotherapy, pain relief and general regimen. When a growth has extended beyond the possibility of its removal together with lymph nodes to which there is evidence of spread it is inoperable but may still be resectable. Improvement of surgical techniques is gradu-

ally increasing the proportion of resectable tumors. But bigger and wider operations are not necessarily better. Frequently resecting inoperable growths results in temporary arrest of the growth of metastases for long periods. Similarly, radiotherapy of a tumor in one part of the body sometimes gives spontaneous regressions of lesions at a distance. Advances in preoperative preparation, supportive measures such as blood transfusions and improved anesthesia and postoperative management have brought multivisceral resections into the category of reasonable procedures no longer to be classified as heroic or desperate. Selection of operative procedures in the advanced cancer patient requires experience and judgment so that pain and misery are not increased and the patient is made more comfortable. In addition to conventional palliative x-ray therapy, radiations from isotopes are useful in management of the patient with advanced cancer.  $I^{131}$  in thyroid cancer with metastases,  $P^{32}$  in the leukemias and  $Au^{198}$  in pleural and peritoneal effusions are coming into general use. In hormone dependent tumors of the breast and prostate, administration of hormones and extirpation of endocrine glands—gonads, adrenal cortex and hypophysis—may give the advanced cancer patient added months of life in comparative comfort. In the reticu-

loses, nitrogen mustards and related cytotoxins may yield further relief after x-ray therapy has become ineffective. Other chemotherapeutic agents are coming into wider use—antifolic acid compounds and those which interfere with the action of ribonucleic acid in the metabolism of the chromatin of the nucleus. In the relief of pain, drugs, anesthetics and surgical procedures are used. Minimal doses of the simplest drugs should be used first. Gradually increased doses and the use of stronger sedatives and finally narcotics are generally required. Among the operative procedures employed as last resorts are nerve-blocking, nerve or nerve root resection, spinal tractotomy and leukotomy. Much can be done for the comfort of the advanced patient in the way of general medical and nursing care. The maintenance of nutrition, correction of anemia, attention to bowels, control of urinary infection, proper care and dressing of fistulas, ulcers and pressure sores, provision of interest in occupational therapy—all can be attended to in the home and will contribute much to the comfort of these patients in the closing stages of this disease. All of the steps in management detailed here require sustained, keen and sympathetic interest of the medical man in charge.

Cox, R.: *The treatment of advanced cancer*. Postgrad. M. J. 34:60-68, Feb., 1958.

### Art and Science of Dying

A patient who is going to die can, today, be prevented from doing so for a long while. The modern physician has the immaculate, aseptic skills that can keep a diseased, half-dead, cancerous body alive, by intravenous nourishment and with the magic of penicillin and round-the-clock special nursing, so long that the doctor may emerge in the eyes of the kin with little resemblance to the wise and understanding family physician of yesteryear. In the picture known to most physicians the kindly, bearded humanitarian sits quietly by the bedside waiting for his little patient to die or recover: the decision is not his. There is hidden ignorance and

sentimentality in the picture, but there is paradoxically great strength, beauty and spiritual dignity implicit in the situation portrayed. Decrease in modern professional dignity and rapport with the bereaved seems in inverse proportion to the efficacy of the medical sciences to prolong life—the new way of dying, by the slow passage via modern medicine.

Anon.: *Life-in-death*. [Editorial.] *New England J. Med.* 256:760-761, April 18, 1957.

### Rapid Palliative Irradiation

Time and morbidity, the main arguments against palliative radiation therapy for carcinoma of the breast, are overcome by the authors through the use of megavoltage technique. They show that fractionation and protraction may not be as advantageous as previously thought. Surgical palliation has often been employed to prevent necrosis and ulceration of the primary tumor and of the metastatic axillary lymph nodes, because palliative radiation therapy requires three weeks to administer and is followed by prolonged morbidity. Hormone therapy offers some control of local lesions and lymphatic spread but is less effective than irradiation. Technique is detailed using the betatron producing 22.5 mev (max.) energy roentgen rays. The entire treatment to the breast was delivered in two consecutive days followed by irradiation of the lymph node areas on the next two days. The doses were increased from an initial 1250 r to 2500 r. The only significant complication was a moderate dry desquamation of the skin which always cleared within the first month. This method of rapid palliative treatment for carcinoma of the breast and its lymph node metastases gives less complications than the conventional palliative surgery and lower dosage, prolonged radiation therapy. The authors, encouraged by the results, are now using the method in less advanced breast carcinomas and suggest the possibility of its advantages as a curative technique.

Cochran, D. Q.; Holtz, S., and Powers, W. E.: *The rapid palliative treatment of breast carcinoma; a preliminary report*. *Am. J. Roentgenol.* 81:479-484, March, 1959.

## Palliation in Breast Cancer

Various androgens are compared for their efficacy in the palliative treatment of advanced cancer of the breast. Testosterone, unesterified, is broken down by the liver into relatively ineffective compounds such as androsterone when taken orally, and when injected is rapidly eliminated. Its elimination is retarded by using testosterone in oil, the common form of androgen therapy for breast cancer. Injections of this androgen must be repeated at intervals of 48 to 72 hours to maintain adequate blood levels. Depots of crystalline suspension and implants give indeterminate duration of action. Phenylpropionate and enanthate of testosterone are of value in maintenance therapy after an adequate blood level has been built up. For oral and sublingual therapy methyl testosterone is used; but it occasionally induces jaundice. Fluoxymesterone (halotestin) given orally is similar in action to methyl testosterone. It gives clinical benefits similar to those of testosterone propionate in the case of bone metastases from mammary carcinoma, and in addition gives occasional spectacular response in soft tissue metastases. The main advantage of halotestin over testosterone phenylpropionate is that it causes little or no masculinization. Fifty patients treated with this new steroid are reported. Some patients responded to halotestin after response to other androgens and corticosteroids had been lost. Response was also obtained in cases of bone metastases when previous x ray-induced menopause or estrogen therapy had failed. Complications noted were: nausea, irritability, diarrhea, ankle edema, headache, increased libido, seborrhea and receding temporal hairline.

Stoll, B. A.: Fluoxymesterone (halotestin) in advanced breast carcinoma. *M. J. Australia* 46:70-74, Jan. 14, 1959.

## Pain in Terminal Cancer

Contrary to popular belief, cancer is not usually a painful disease. Primary lesions are often so painless that they grow to considerable size before attracting attention.

However, in the terminal stages the pain may be severe owing to involvement of bone, liver or some part of the central nervous system. In no field of practice is it more apparent that medicine is an art than in the management of pain from cancer. The physician, as soon as he is convinced that recovery is impossible, should devote all his art toward making the patient's remaining life as pleasant and pain-free as possible. He need feel no restriction in choice of drugs for fear of subsequent addiction. Local pain is best treated locally. Pain from single deposits in bone and pain of carcinoma of the bronchus are responsive to high voltage therapy. Intractable pain of nerve origin is relieved by chordotomy. When general analgesics are required, it is advisable to start with simple, nonhabit-forming drugs, as those containing aspirin, codeine, phenacetin and caffeine. After these milder drugs lose their effectiveness, more powerful ones can be employed in gradually increasing dosage as indicated. Finally morphine and its derivatives will have to be used. The patient with incurable cancer in the terminal stage should be kept free from pain, even if this means keeping him practically unconscious.

Hancock, P. E. T.: *The relief of pain in terminal cancer. Practitioner* 179:326-328, Sept., 1957.

## Surgical Relief of Pain

If neurosurgical methods of pain relief are to be used they should be applied before the onset of drug addiction. If not, the patient is particularly hard to manage and may still require narcotics after a pain-relieving operation for psychic effect. The surgical approach to the problem of intractable pain is based on the knowledge that pain as a sensation is transmitted from the site of origin through fairly well known pathways of the peripheral and central nervous systems and that surgical interruption of these pathways should lead to relief. Pain-relieving operations should be suggested when it is obvious to the physician that the condition causing the pain cannot be cured or alleviated by direct attack and that mild analgesics, as the salicy-

lates with codeine, cannot control the pain. A presumed life expectancy of several months is desirable. Most operations for relief of pain can be done with local anesthesia supplemented with very light inhalation or intravenous anesthesia; many with local alone. Therefore, only reasonably good general physical condition of the patient is necessary. Chordotomy is the most valuable and widely used procedure for the surgical control of pain. Rhizotomy has the disadvantage of complete loss of sensation and of the risk of disturbing the circulation of the spinal cord. Neurosurgical procedures in many instances can be of help in relieving the patient's pain without much loss of function. They should be done early.

Wetzel, N.: *The surgical relief of intractable pain.* S. Clin. North America 39:245-252, Feb., 1959.

### Palliative Radiation

Survival time alone is not an adequate measure of the palliative value of radiation therapy. Prolonged survival with continued or increased suffering is not desirable. The relief of pain and discomfort, the healing of ulcerative lesions, the lessening of hemorrhage and infection, repair of pathologic fractures and healing of metastatic lesions in bone, eradication of cough and dyspnea, the restitution of sleep and delay in the generalization of the cancer are among the benefits that can be expected as indicative of satisfactory palliative response. Radiation therapy may be considered in any advanced lesion in which the general condition of the patient is satisfactory and in which such therapy can be given without undue hardship. The author makes a plea for the reevaluation of the present ideas concerning the management of the cancer patient to include effective palliation. The patient and the family must be educated to accept palliation in cancer as they do in other incurable chronic diseases—nephritis, hypertension, diabetes, arteriosclerosis and chronic heart disease. Group consultation is of utmost importance in palliative as in curative therapy. Palliative management of the incurable cancer patient should be decided by con-

sultation among the family physician, the surgeon, the radiologist and the pathologist. Only the cachectic patient in a terminal state is to be considered hopeless. All others are proper candidates for planned palliative therapy.

Shoss, M.: *Palliative radiation therapy; use in the advanced cancer patient.* Missouri Med. 55:849-853, Aug., 1958.

### Saline Lobotomy

Fractional injection of physiological saline solution into the frontal lobe gives less untoward effects than surgical prefrontal lobotomy or the injection of procaine or alcohol to produce frontal lobe interruption in the relief of intractable pain of cancer. Injections of saline are made through bifrontal burr holes. Antibiotics are given postoperatively. When repeated injections of one frontal lobe, no longer produce observable effects, the opposite frontal lobe is injected. Twelve patients were selected for this procedure according to the usual criteria for lobotomy: (1) pain too extensive for chordotomy or other pain relieving procedures, (2) drug addiction, (3) pronounced situational depression. No complications of infection, hemorrhage or seizures were encountered. Occasionally a patient was briefly uncommunicative. Satisfactory pain relief was obtained in all twelve of the patients. Alteration of the patient's condition becomes apparent with relaxed attitude, less fear of passive movement, increased interest in food and surroundings, more voluntary movement in bed or ambulation and more self help and cheerfulness. The patient is not disturbed by the procedure, and when it is necessary to repeat the injections at close intervals there is no objection or fear. The number of injections required is determined by the persistence of the symptoms, the intensity of the pain, the severity of the disease and the life expectancy. The simplicity and effectiveness of this procedure make it a valuable tool for the relief of pain in the patient with advanced or extensive cancer.

Bridges, T. J., and Liss, H. R.: *Saline lobotomy for relief of pain due to advanced cancer.* Cancer 11:322-325, March-April, 1958.



## Palliation in the Home

Surgical and radiological palliative procedures usually require hospital facilities. But much effective palliation—especially that of pain relief—may be given the patient under home care. Too often the psychological aspects of palliation are overlooked by the attending physician. The patient who has undergone amputation, laryngectomy, colostomy, disfiguring head, neck or breast surgery requires special psychological management to prevent states of deep despair. The inoperable patient must be reassured that everything possible is being done and he must not have taken away all hope for long survival. The palliative treatment should include attention to correction of anemia by transfusion, of nutritional deficiencies by administration of vitamins, and of infections by judicious use of antibiotics. Androgenic and estrogenic hormone therapy may give increased length of life to the patient with cancer of the prostate or breast, and it is important to remember that these hormones may completely relieve the pain of bony metastases which has been refractory to all narcotic drug therapy. Occupational therapy diverts the attention of the advanced cancer patient and helps to combat fear, suffering and depression. In the treatment of pain, since drugs are often needed over long periods, the smallest amount of the weakest drug that will give relief should be used first. Many patients can be carried for a long time on aspirin, phenacetin and amidopyrine combinations, supplemented as needed with a barbiturate or with chloral hydrate. Demerol, codeine and finally morphine or one of its derivatives may be needed. Thorazine in 10 mg. doses every four hours often allows marked reduction of morphine dosage.

*Bianco, A. A.: The home care of a cancer patient. New York J. Med. 58:3509-3511, Nov. 1, 1958.*

## Palliation of Effusion by Talc

In the opinion of the author, radioactive colloidal gold and nitrogen mustard control pleural effusion by producing ob-

literative pleuritis rather than by their cancerocidal action. Accordingly, he deliberately caused adhesive pleuritis in thirty cancer patients by instillation of talc into the pleural cavity. A similar technique—pleural poudrage—has been used for more than 20 years for the production of adhesions in recurrent spontaneous pneumothorax and preparatory to extrapleural pneumonolysis. In the present series of 30 patients, effusion was successfully controlled in 27. There was incomplete control in the remaining three and thoracenteses were needed later. Reports of success with nitrogen mustard and radioactive colloidal gold vary from 50 to 70 per cent. The procedure is carried out under local and intercostal block anesthesia. A catheter attached to a water-trap bottle is introduced through the fifth or sixth interspace in the midaxillary line. The autoclaved powdered talc, suspended in 1 per cent procaine solution, is injected into the catheter which is clamped while the patient is turned in various positions to distribute the talc. The tube is left in place until drainage ceases—usually about three days. It is then removed and the mattress suture, laced at the time of intubation, is tied at extubation and the patient discharged. This procedure of intercostal intubation and talc instillation merits further clinical trial in comparison with the older deep x-ray therapy and multiple tap and with the newer use of radioactive gold and nitrogen mustard.

*Chambers, J. S.: Palliative treatment of neoplastic pleural effusion with intercostal intubation and talc instillation. West. J. Surg. 66:26-28, Jan.-Feb., 1958.*

## Palliation in the Aged

In the management of geriatric cancer the physician must decide, in each case, which of three courses is to be followed—to cure, to palliate or to endure. To *cure* involves complete eradication by surgery or by radiation without recurrence for a period of five or ten years. To *palliate* is to live with the situation on a somewhat compromised basis, with adjuncts of surgical, radiation and hormonal therapy. There is temporary easement with an eventually grave outlook. To *endure* is all

that can be done when to cure and to palliate are no longer possible and the situation is hopeless. Individual patients from the author's practice are described with many references to palliative procedures in incurable cases. In spite of palliative radiation following surgical removal of a breast cancer that had been secreted for several years, the patient's condition became rapidly worse and she soon died. Many elderly patients refuse operations for cancer, leaving palliation as the only course of management. A woman in her early nineties with primary carcinomatous papilloma of the bladder and primary cancer nodules in both breasts, following successful fulguration of the bladder tumor, refused injection estrogenic therapy for the breast cancers. She consented to take three pills a day and no more. Oral androgen, 10 mg., morning, noon and night gave regression of the mammary masses, so that in two years they left only geographical dimples. The patient died of cardiac causes after three years. With effective palliative management life can be full and sweet and long in spite of breast cancer. Palliative radiation therapy carried a patient with carcinoma of the large bowel from his sixties into his seventies, but then the tumor changed from radiosensitive to radioinsensitive. Similarly sensitivity to chemotherapeutic drugs gradually changes to a condition of resistance. The author refers to a patient in her eighties, with rectal cancer returning to his office, after a fling with a miracle serum, depleted in cash, deflated in spirit, denuded of flesh and thoroughly whipped. Palliative operation with colostomy gave the patient three and a half years more of life. Opiates, barbiturates and demerol all failed to palliate pain in a patient operated upon for ovarian carcinoma. In desperation the author prescribed thorazine which gave the patient comfort for the rest of her life. A man in his mid-sixties with myelogenous leukemia, treated palliatively with radiation and chemicals, responded with remissions and exacerbations until he reached his seventies. In addition to surgical and radiation palliation, chemotherapy with hormones and nitrogen mustard

is coming into wider use in lengthening the lives of incurable cancer patients and in making their last days more tolerable.

Ross, C. H.: *Cancer in geriatrics. J. Michigan M. Soc.* 57:536-545, April, 1958.

## Hormone Palliation in Breast Cancer

Destruction of the pituitary represents the most recent advance in the palliative treatment of advanced carcinoma of the breast. Although hormones do not cause cancer, they are associated with its progression. Alterations in the endocrine balance can produce profound changes in the behavior of certain neoplasms, especially those of the breast and prostate. The pituitary, governed by the hypothalamus, controls breast development by two groups of hormones: (1) prolactin and growth hormone, which act directly on breast tissue and (2) gonadotropins and adrenocorticotrophic hormone (ACTH), which act upon the ovaries to produce estrogens and progesterones, and upon the adrenal cortex respectively; thyrotrophic hormone (TSH) from the pituitary also acts on the breast through its effect on the thyroid. Secretion of endocrine may be controlled by chemical suppression of the pituitary by administration of certain hormones or by operative removal or destruction of the sites of production of the offending substances. Approximate percentile remission rates of breast cancer by the several current methods of hormonal treatment are as follows: administration of testosterone, 25 premenopausal, 19 postmenopausal; prednisone and thyroid, 50; estrogens, 6-14 premenopausal, 29 postmenopausal; oophorectomy, 25 premenopausal, 2 postmenopausal; adrenalectomy, 50; hypophysectomy, 57. Complete surgical hypophysectomy is difficult and the author substituted radiological hypophysectomy by transfrontal insertion of yttrium-90 in wax, a pure beta emitter with 68 hour half-life and 1 cm. tissue penetration. In cases with blood-born metastases 87 per cent remissions were obtained.

Edelstyn, G. A.: *Hormonal control of breast cancer. Irish J. M. Sc.* 6th Ser. No. 393:428-431, Sept., 1958.

## Palliative Prosthesis in Esophageal Cancer

The author designed a rigid plastic tube for peroral insertion through malignant tissue of the esophagus which obviates the necessity for gastrostomy or jejunostomy. The tube is inserted through the esophagoscope under topical or inhalation anesthesia. It is flanged so that it cannot drop into the stomach or rise into the mouth. This tube permits prompt feeding and allows early x-ray treatment. Gastroscopy in inoperable, unresectable carcinoma of the esophagus gives no significant extension of life and 30 per cent have complications; the majority have complications, minimal palliation and remove the tubes wilfully. For satisfactory nutrition is possible only when patients are esophagectomized and an artificial or surgically constructed esophagus is made. The author's tube installed primarily in inoperable, unresectable esophageal cancer appears to be an advance in the management of these difficult patients. Four patients treated with this prosthetic device are reported. The average survival was four months after insertion of the tube. There was marked palliation in regard to deglutition of liquids and solid food.

*Sachs, L.: A plastic prosthesis for palliating carcinoma of the esophagus. Surgery 45:377-388, March, 1959.*

## Chemotherapeutic Palliation

With the possible exception of the action of aminopterin in chorionepithelioma, chemotherapeutic agents have only palliative and not curative effects in human cancer. Although several types of transplantable cancer in animals can be completely destroyed by systemic chemotherapy, no chemical anticancer agent has given such curative effect in cancer in man. The effects of chemotherapeutic agents in human cancer are feeble but several available compounds give favorable palliative responses, especially in the leukemias and Hodgkin's disease. The agents most widely used are nitrogen mustard, 6-mercaptopurine, 6-thioguanine, 6-chloropurine, amethopterin, aminopterin, adenopterin,

azaserine, triethylenemelamine, triethylenephosphoramide, triethylenethiophosphoramide, myleran and chlorambucil. Chemotherapeutic compounds are administered orally, intravenously, into the pleural and peritoneal cavities, intra-arterially and interstitially into the tumor itself. Beneficial effects of these compounds are temporary; cancer cells appear to be able to adapt themselves to repeated chemical injury. It is reasonable to hope that the length of the periods of palliation can be increased by more effective products and that eventually a chemical cure for at least some of the forms of human cancer will be developed. A single substance which will specifically inhibit the growth of all cancers and have little or no effect on normal tissue is not likely to be found, for cancer is probably not one but many diseases.

*Pigott, J. D.: Chemotherapeutic agents in the palliative treatment of cancer. J. Tennessee M. A. 52:45-49, Feb., 1959.*

## Subarachnoid Block in Cancer Pain

Subarachnoid alcohol block as used twenty years ago to control pain in patients with cancer yielded analgesia lasting only about six weeks. This led to the use of the neurosurgical measures, rhizotomy, tractotomy and lobotomy. Recently there has been a return to subarachnoid block by alcohol, phenol or ammonium sulphate. It was shown that the neurosurgical measures carried more risks than alcohol block; however, these risks may be justified in the presence of prolonged suffering from pain resistant to subarachnoid block alone. When 95 per cent alcohol comes into contact with nerve tissue the nerve fibers are destroyed. When it is injected into the subarachnoid space it produces chemical rhizotomy. The author uses subarachnoid alcohol block in patients with advanced disease whose condition would not permit radical procedures, and in those patients in good general condition with pain of short duration (four to eight weeks of continuous pain), and with life expectancy of more than one year. Of 95 patients with severe pain from malignant neoplastic disease treated with this

technique, 57 had complete relief from pain for from two weeks to a year or longer, 32 had partial relief and 6 had slight or no relief. Paresis, weakness or incontinence occurred in 10 patients. Nine of these recovered from these complications within two months after the alcohol injection. The tenth patient died from progression of her disease two weeks after the block. It is concluded that subarachnoid block is valuable in the management of pain from malignant neoplastic disease, that the procedure is attended by risks and that it should be undertaken only by physicians trained in nerve block techniques.

*Perese, D. M.: Subarachnoid alcohol block in the management of pain of malignant disease. A. M. A. Arch. Surg. 76:347-354, March, 1958.*

### **Palliation in Lung Cancer**

The results of surgery for carcinoma of the lung are very poor. Five-year cures by surgery or by deep x-ray therapy are so rare that both these methods for practical purposes should be regarded as palliative only. Radiotherapy after apparently successful surgical therapy is not indicated. Results of radiotherapy before surgery, to make an inoperable case operable are not very encouraging. Chemotherapy, sometimes combined with radiotherapy, may help to inhibit metastatic growths. Management of the inoperable and terminal case is much the same for cancers of all sites. A great deal can be done for this group of patients, but this management is much more difficult than the resection of an operable growth. Any doctor can treat a curable disease; but it takes a very good medical man indeed to treat chronic incurable disease well. Sometimes, unfortunately, the incurable patient, following operation, returns to the surgeon stating that his doctor said he "can do nothing for me," and the specialist surgeon then must take responsibility for management. When there is absolute proof of cancer, always tell the relatives and warn them to tell nobody else, or it will later come round to the patient. Never give the patient a specified time to live. Definite prognoses are always wrong and do much harm. When pushed for an answer, guess weeks,

months or years whichever seems most likely. Never tell the patient himself that he has cancer unless he looks you straight in the eye and asks point blank. Then, if you have absolute proof, say yes at once, because he is mentally ready for the affirmative answer and will be less unhappy with definite bad news than with indecision. The patient should continue his work as long as possible. Warn the patient that he will need a prolonged period of supervision and treatment, and that during this period his symptoms—cough, pain, etc.—will be controlled by medicines. Do everything possible to get him to accept his limitations and maintain his life. Keep him convinced that you are still interested in every detail of his care and confident that, whatever symptoms come up, you will do something about them. The author avoids, as far as possible, all sedatives such as barbiturates. They cause mental depression and gloomy foreboding. He also avoids the various tranquilizers, which are apt to cloud the judgment. Opium alone puts on the proverbial rose-colored spectacles. The author's sheet anchor prescription is: tincture of opium 15 minims, camphorated tincture of opium 15 minims, chloroform water to two drachms. The patient is told that this medicine is quite harmless and can be taken as required, double doses at night and repeated during the night if necessary. The patient is warned that the only troublesome effect is constipation that can be relieved by agarol regularly in whatever dosage he finds necessary. This mixture becomes the elixir of the gods to patients. They begin to smile, to eat more and to do more. It is not a form of euthanasia; it prolongs life. Near the end, when they are bedridden, it produces the calm detachment of the opium smoker, so that they fade peacefully away. They realize that their days are numbered, but the opium makes it seem of no particular importance. They may talk about death with calm acceptance. Others imagine they will get better right up to the end.

*Haward, J.: Some observations on the pathology and treatment of carcinoma of the lung. M. J. Australia 46:14-17, Jan. 3, 1959.*



# Keeping up

## Mechanism of Cancer Death

Death from cancer need no longer be considered as due to mechanical interference with a vital function or to hemorrhage and infection. Knowledge has increased to embrace the concept of cancer as a systemic or biochemical disease, radiating initially from a single focus but later from metastases as well. The cause of death from far advanced cancer is an extensive derangement of normal biochemical functions similar to those occurring in sepsis. The malignant cachexia of the advanced cancer patient undoubtedly influences the host in a great variety of subtle biochemical ways, as does extensive sepsis. Anorexia and starvation play prominent roles in the pathology of advanced cancer. Biochemical derangements preclude the effective metabolic utilization of ingested nutrients. Today's cancer management is surgical, radiological or chemotherapeutic. Perhaps in the near future, when the natures of the demonstrable biochemical lesions of cancer are explained on a molecular level, practical immunological attacks against malignant disease may be developed. It is quite possible that, long before we have a chemotherapeutic agent that will eradicate the tumor itself, agents will be found to protect the host cells against the biochemical aggression, thus achieving long-range palliation.

*Hardy, J. D.: Why do cancer patients die? [Editorial.] Surg., Gynec. & Obst. 108:368-369, March, 1959.*

## Pathogenesis of Tissue Malformation

To date the filterable tumor agent is the only success to encourage those stubborn adherents to simple theories of cancer and

its causation who persist in believing that they are dealing with a specific disease rather than a generic appellation. And not a single human invasive tumor has been shown to be due to a virus. In cancer research, emphasis has swung away from the old search for one specific growth substance, responsible for a definable disease entity, toward an attempt to understand why cell populations in living organisms are so changeable that they may become independent of almost every known kind of stimulation and inhibition. Dependency and autonomy are both relative and quantitative. Instead of trying to find what chemical turns a normal cell into a cancer cell, search is being made for the factors which in complex organisms transcend the cell to unify and control a mass of protoplasm into orderly development and maintenance of a whole, for intracellular mechanisms of synthesis chiefly concerned with growth and differentiation, and for ways the interplay between these two, without which there is no life, becomes disturbed so that tissue malformation occurs. Search is being made for the inherent mechanisms that allow tissues once involved in this process to progress further and further away from dependence on normal organismic controls toward independent expressions of their modified potentialities to form a new whole. Complicated but detailed explanations of these processes in terms of organization and its disturbances will some day be at hand. Meanwhile we have no right to expect any civil answer at all to the question "What is the cause of cancer?" In clinical cancer we deal with a variety of abnormalities of growth and differentiation, due either to inherited defects or to abnormal environments and



# *with Cancer*



manifest as changes in growth, degree of differentiation and in tissue position or blending. We are concerned with transmissible defects such as those leading to retinoblastoma, intestinal polyposis or xeroderma pigmentosum; and also with acquired malformations such as those of tissue arrest during development leading to nephroblastoma, of displacement leading to melanoma, of blending leading to hamartoma, and of over stimulation from without, leading to skin tumors, or from within, leading to tumors of the thyroid or of the bladder. These malformations occur in a bewildering variety of graded manifestations. Hyperplasia blends imperceptibly into neoplasia. Benign and malignant are but convenient terms of relative prognostic value. Benign tumors may give rise to benign, fully functioning metastases. Malignant tumors may give rise to benign metastases, and benign tumors may possibly give rise to malignant metastases. We talk in curious mixed terms of carcinoma in situ, of pre-invasive cancer, of malignant adenoma, of benign metastasizing tumors, and even of non-lethal cancer morphologically indistinguishable from the lethal form. We persist in providing convenient labels for these observations which do not fit in with our outmoded view of cancer as a sharply defined disease entity. The basic theory should be regarded with the utmost suspicion. The whole gamut of abnormality of growth, progressive and regressive, is involved. The wonder is not that tissue malformations and disorganization sometimes occur, but rather that, in the complexities and turmoil of growth, development, repair and maintenance going on continuously in all living creatures, we retain a

recognizable and functioning form at all. By merely moving the point of diagnosis on our scale of growth disorder the word "cancer" can be made to represent a more and more serious disease, until by definition it is always fatal; and by shifting our ground in the opposite direction we can produce figures to show that our treatments are continually improving—now a popular sport among some surgeons and pathologists. All the many definitions of cancer deal with the behavior of cell groups in terms of deviation from normal patterns, none of which is peculiar to cancer. We are not dealing with a specific disease but with one end of a scale of changes in several tissue behavior patterns from which have been arbitrarily singled out cases which demonstrate enough deviation from the normal to justify us in giving them collectively a single name. The public view of the pathogenesis of cancer is quite unreal, being governed by fear and hope instead of by knowledge and understanding. This view is supported by the press which seeks sensation and by those requests for money which use either fear or the promise of a simple and early solution as the basis for appeal. Continuing talk about one day discovering both the cause and the cure of a terrible disease called cancer keeps people ignorant of what is known and misled about what is possible. The medical profession, but a special category within the general public, is infected with the same ideas, influenced by its own propaganda and biased by its own aspirations. Our journals erupt in frequent statements about cancer education and cancer diagnosis, cause and cure; about the answer which is just around the corner and about chemotherapy which

will solve all problems—muddles and myths which we create for ourselves. Linguistic analysis will not solve our difficulties but may help us to see our problems more clearly. The word cancer vaguely covers the most disorganized of the tissue malformations and is applied according to individual preference on the basis of selection of those degrees of change giving rise to the greatest danger to life of the organism. Since the term cancer can have no precise boundaries this side death, it would be better if we were to abandon its use in communications having some pretense to scientific reporting. "Cancer" is to the neoplastic disorder what "galloping consumption" used to be to the infections—it is merely less precise. The next generation may well wonder how we came to retain this term so long in our medical journals when the Victorians managed to confine their own particular, terrifying, end-of-scale bogey to their novels.

*Smithers, D. W.: On the pathogenesis of cancer. Lancet 1:589-593, Mar. 21, 1959.*

### Lymphosarcoma in Children

The term lymphosarcoma generally refers to all primary malignant tumors of lymphoid origin except Hodgkin's disease and includes three types: (1) giant follicle lymphosarcoma, (2) reticulum cell sarcoma, and (3) lymphosarcoma. Giant follicle lymphosarcoma is relatively benign and includes both the characteristic giant follicle formation and lymphosarcoma that has largely retained follicular features. Transition to the other two classes is common, and borderline growths are often difficult to distinguish. In reticulum cell sarcoma the predominant cell is more than one and a half times as large as the mature lymphocyte. Lymphosarcoma is more common in boys than in girls. The male-female ratio is 4.5 to 1 at ages 11 to 15 years and approaches unity in the very young or old. Symptoms of abdominal tumor appear first in almost a fourth of children, about twice as often as in adults. Intussusception may result. Other presenting manifestations are enlarged lymph nodes in axillary, inguinal, mediastinal or

other sites; lesions in bones, the nasal or oral pharynx and skin or subcutaneous tissue; and pleural effusion. Lymphosarcoma is often more locally active in children than in adults. Chest plates show tumor in more than half of patients and mediastinal or hilar adenopathy in more than a third. Bone lesions generally appear osteolytic rather than osteoblastic, although types may actually be mixed when one or the other is more apparent in films. Treatment with radiation, the basis of management, may relieve distressing symptoms and save life, at least for a time. For specific problems such as superior vena caval block, polyfunctional alkylating agents are administered before radiation to reduce congestion and neoplastic growth. Antimetabolite drugs, principally folic acid antagonists, are given chiefly when acute leukemia develops. Intermitent treatment with amethopterin may prevent leukemic transition when lymphosarcoma is localized. Supportive therapy may include blood transfusion, antibiotics, parenteral fluids and operation to relieve upper tracheal or intestinal obstruction.

*Rosenberg, S. A.; Diamond, H. D.; Dargeon, H. W., and Craver, L. F.: Lymphosarcoma in childhood. New England J. Med. 259:505-512, Sept. 11, 1958.*

### Colon and Multiple Cancers

Human cancer is almost always solitary, suggesting development of a possible resistance in a person with one cancer to another. This singleness of cancer in man is more impressive than its less than 2 per cent plurality. Analysis of 4800 consecutive autopsies revealing a total of 1514 visceral cancers showed the following multiple primary cancers: four triple, 14 double of different systems and six double of the same system. Of these total 52 multiple cancers the colon and rectum were the origin of more than twice the number in any other site: colon and rectum, 13, lung six, uterus five, breast five, kidney five, ovary four, prostate four, stomach two, pancreas two, tonsil two, small intestine one, thyroid one, larynx one and ampulla of Vater one.

*Fried, B. M.: Primary multiple cancers. A.M.A. Arch. Surg. 77:730-741, Nov., 1958.*

# "You Are Standing at the Bedside of a Patient Dying of Untreatable Cancer"

Edward H. Ryneerson, M.D.

Because I wish to personalize my remarks and define my parameters, I have adopted a title which emphasizes that I address myself to the *INDIVIDUAL* physician who is seeing an *INDIVIDUAL* patient dying of a cancer for which every conceivable avenue of treatment has been explored with total failure, and this patient, moreover, is suffering excruciating pain and is pleading for release. There are too many instances, in my opinion, in which patients in such a situation are kept alive indefinitely by means of tubes inserted into their stomachs, or into their veins, or into their bladders, or into their rectums—and the whole sad scene thus created is encompassed within a cocoon of oxygen which is the next thing to a shroud. Certain tissue cultures have kept cells living for so many years that they have fulfilled their usefulness and have been thrown out; we have used much of the information thus gained in an inverse manner, meaning that with all the fluids, vitamins, electrolytes, protein supplements, antibiotics, hormones and other agents available to us now we can keep people suffering for an indeterminate number of months. Moreover, although the point is not related to the subject of cancer, we all know of many instances in which persons have been kept alive for years in a near-decerebrate state after massive damage to the brain caused by a stroke, an injury or infection.

The present piece has nothing to do with euthanasia, nor am I talking about any patient in whom there is any question as to the diagnosis. I refer to the patient who is almost in extremis; this unfortunate state has been established beyond any doubt, for the physician and his associates are in unanimous agreement, and there is

no question in anyone's mind as to the prognosis. This patient already has undergone surgical exploration, chemotherapy, radiation therapy—and perhaps, also, if the resources of surgery have been pushed to the ultimate—castration, adrenalectomy and hypophysectomy. Despite all the impressive ministrations science can provide, he is still dying and is still suffering. There simply is no other treatment to apply now, for there is no treatment for death (and may I add that in my opinion many of the so-called extraordinary measures are not often indicated). Neither can the true physician bolster the onus of his own doubts and uncertainties by transferring them to the shoulders of the dying person's relatives or friends.

Once the physician and his associates are in agreement on these matters, the time certainly has arrived for a very frank discussion with the patient's relatives. Almost never am I met with any lack of understanding on the part of these relatives; almost never do they wish to have their loved one maintained indefinitely in a tragic interlude of more and more suffering. Not only that, but in most instances, the patient, who by now has a full understanding of the factors involved, usually is asking for relief of pain, not prolongation of distress.

If neither the patient nor the relatives express a wish for "heroic measures," then who does ask that these be used? Is it the patient's church? So far as I know, there have been no voices representative of the Roman Catholic or Greek Orthodox churches or of the Jewish or Protestant faiths to suggest that physicians should try extraordinary means to keep life going when every process of the body is bent toward extinction. His Holiness, Pope Pius XII, issued an encyclical within the

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last year of his life which stated the official position of the Roman Catholic church as not requiring the physician to use extraordinary means when only certain death and suffering lie ahead. Some comments from the Roman Catholic standpoint are to be found in *Preserving Life*. In an effort to answer the question, "How much does God demand that I do in order to preserve this life which belongs to God and of which I am only a steward?" Father Kelly writes: "The physician is obliged to use ordinary means; as for extraordinary means, he may use them if he wishes, but, apart from very special circumstances, he is not obliged to do so . . . I might add here that the relatives do not make this decision precisely in their own name, but rather as representing the patient; hence, they should try to determine what he would reasonably want done under the circumstances . . . If other means are lacking for determining this, the golden rule would be helpful. What would the doctor himself want if he were in the patient's condition?"

"When a doctor and his consultants have sincerely judged that a patient is incurable, the decision concerning further treatment should be in terms of the patient's own interests and reasonable wishes, expressed or implied. Proper treatment certainly includes the use of all natural means of preserving life (food, drink, etc.), good nursing care, appropriate measures to relieve physical and mental pain, and the opportunity of preparing for death. Since the professional standards of conscientious physicians vary somewhat regarding the use of further means, such as artificial life-sustainers, the doctor should feel free in conscience to use or not use these things, according to the circumstances of each case. In general, it may be said that he has no more obligation to use them unless they offer the hope of some real benefit to his patient without imposing a disproportionate inconvenience on others, or unless, by reason of special conditions, failure to use such means would reflect unfavorably on his profession."

If there is no demand for the prolongation of life and suffering on the part of the patient, the patient's relatives, or the pa-

tient's spiritual adviser, then who is it who causes these extraordinary measures to be continued indefinitely? The answer, I believe, is that in most instances it is the physician himself, and thus this presentation of mine is addressed to members of my own profession. It is a paradox that while death is singularly an individual phenomenon, our attitude toward it, in the largest measure, is based on the effect of death upon others. Death is a social event. Thus the care provided to a dying patient implicitly includes a consideration of the living—family, friends, society. Dying, then, for the most part, takes into consideration the feelings, attitudes, values and beliefs of the living. For that reason, frequent resort is made to measures which ostensibly disregard the dying and serve the living. Actually, however, both the living and the dying often are disregarded, for deference is paid to ritualism devoid of consideration for actual feelings. In a situation of the dying patient, one has to consider:

1. The philosophies of the one who is dying, of the living family and of the medical attendants.

2. The fact that society itself has traditional values which are accorded to life and death and which must be taken into account; however, these values should be of less importance than those very personal values as decided by the patient and his family.

3. The fact that there are certain unconscious elements, such as the feeling on the part of some relatives that they are somehow guilty in the presence of impending death, and that this ill-founded sense of guilt needs to be defended by prolongation of the life of the victim; superstitions may be at hand which need to be propitiated, or a personal anxiety born of a relative's identification with the dying person may need to be ameliorated somehow.

One must also remember that religious values interwoven in the process of death sometimes are viewed in different ways:

1. In some cases death is viewed as a punishment—an end, rather than a beginning.

2. In other cases death is accepted as a natural terminus—simple, factual, unemotional.

3. Sometimes death is viewed as a reward—a beatific vision, union with the eternal and so on.

It need not be emphasized here that all cultures, from the most primitive to the most advanced, have death rites and that in our country these rites can take all forms, for we have at least the residuum of all cultures.

What then should be the components of the care of the dying patient?

1. He should die with dignity, respect and humanity.

2. He should die with minimal pain.

3. He should have the opportunity to recall the love and benefits of a lifetime of sharing; he and his family and friends should visit together, if the patient so wishes.

4. He should be able to clarify relationships—to express wishes—to share sentiments.

5. The patient and relatives should plan intelligently for the changes which death imposes upon the living.

6. The patient should die in familiar surroundings, if possible; if not, then quietus should take place in surroundings made as near homelike as possible.

7. Finally, but importantly, there should be concern for the feelings of the living.

If these two things are certain: first, that the patient is dying of a malignant process for which there can be no treatment, and second, that the patient, his relatives and his spiritual adviser are aware

of the situation, then what I am suggesting is that the physician should do all he can to alleviate the patient's suffering and make no effort to prolong his life.

In discussing this conviction, I have received three comments or questions. The first is: "You are trying to play God." I reject this charge, for I believe that it is actually the physician who, by using extraordinary measures, prolongs life and suffering is the one who "plays God."

Second is the query: "What do physicians do?" Well, that has been answered innumerable times, and many of the instances in question are in my own practice and among my own friends. Most physicians do not ask for anything more than kindness and comfort; they are likely specifically to oppose "heroic measures."

Every physician worthy of the name shrinks from the "I:it" relationship with his patient and, rather, embraces the "I:thou" apposition, for his daily labors remind him only too forcefully that one day he, too, may be the patient.

Third is the question: "What would you do if this occurred in your own family?" I have had the answer to such a problem for some years gone by, for the travail and misfortune I am speaking about did occur to a member of my immediate family. We kept her in her own bed in her own home and made certain she suffered as little as possible until she was released by death.

I conclude by saying that when I am at the bedside of a patient dying of untreatable cancer, I make the decisions I have recorded here. But now YOU are standing at another bedside and YOU must make YOUR decision.

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### **"Without a Groan, Almost Without a Fear"**

With incurable cancer in the terminal stage the patient should be kept pain free, even if this means keeping him practically unconscious. There can be no excuse for allowing patients to suffer unnecessarily once the diagnosis has been made, and the inevitability of an early death is apparent.

*Hancock, P. E. T.: The relief of pain in terminal cancer. Practitioner 179:326-328, Sept., 1957.*



# Prevention of Occupational Cancer Hazards

*W. C. Hueper, M.D.*

Cancers, like other diseases, are not manifestations of spontaneously developing abnormal cellular functions but are reactions to specific pathogenic agents present in the internal or endogenous-constitutional (hereditary, congenital, acquired), and external or inanimate (chemical, physical) and animate human environment. Observations made in the past on factors underlying carcinogenesis in man and animals indicate that agents of both the internal as well as the external human environment play a part in the causation and development of cancers, as they do in all other environmental diseases. If the amount and significance of the available factual and near-factual data concerning the two types of carcinogenic agents are critically assessed, it becomes evident that the information on the various endogenous factors incriminated in this respect is, with the exception of certain hormonal disturbances, rather meager and insecure. From the viewpoint of cancer prevention it is, moreover, important that past experiences with a preventive control of constitutional diseases of different types have demonstrated the great difficulties encountered in the development and institution of practicable and effective measures against diseases of primary endogenous origin. Defective information and methodologic complexities thus do not favor, at the present time and under the existing circumstances, an enlightened and serious interest in the endogenous aspects of cancer prevention.

In contrast, a great deal of more or less well established and specific factual evidence has accumulated over the past century concerning diverse exogenous carcinogenic agents, the various sources of exposure to them, the types of individuals and population groups involved and the site and character of precancerous and

cancerous reactions elicited by them. Through attempts directed at controlling cancer hazards of external environmental origin undertaken for a number of years mainly in specific industries some practical, while usually limited, experiences in the use of preventive measures of various types have been gained. It appears thus that the information available on cancer hazards related to external environmental agents furnishes some of the prerequisites essential for the development of a comprehensive cancer control program based on methods of primary prevention which have been demonstrated to be practical and effective when applied on a limited scale.<sup>1, 2</sup>

Cancer prevention programs may be developed on several general principles. They may be of comprehensive nature or may be restricted to one, a few, or many aspects encompassing a particular principle.

## General Basic Principles for Cancer Prevention Programs

1. Environmental carcinogens, according to physicochemical characteristics, either as single agents, such as beta-naphthylamine, or as groups of related agents, such as aromatic amino- and azo-compounds, or as large general groups, such as various types of radiation, or inorganic or organic chemicals or polymers, or as the totality of all known, recognized, suspected and potential environmental carcinogens following cancer hazards associated with the individual agents from their sources of original occurrence or production, through those related to packing, handling, shipping, processing, using and consuming.

2. Environmental carcinogens according to general types of exposure, such as:

- (a) Occupational — professional — industrial agents.

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(b) Dietary agents: additives, contaminants, natural constituents, processing products, coating, packaging and wrapping materials and inadequacies (hypothyroidism, hepatic hypo- and dysfunction, etc.).

(c) Consumer goods: cosmetics, over-the-counter drugs, rubber goods, sanitary and household goods, contraceptives, paints, solvents, fuels, pesticides and other environmental poisons.

(d) Medicines: synthetic and natural chemicals, metal and plastic implants, human tissue implants and plasma sterilized with betapropiolactone, ultraviolet and x radiation and radioactive substances.

(e) Habits, hobbies and customs: smoking, chewing and snuffing tobacco, betel nut and khaini quids, chutta, kangri, kairo, kang, dhoti, noncircumcision and sun bathing.

(f) Water, air and soil pollutants, natural and artificial: aliphatic and aromatic hydrocarbons, arsenicals, radioactive materials and selenium and environmental factors, ionizing radiation and ultraviolet radiation.

3. Environmental carcinogens according to specific routes of exposure: cutaneous, respiratory, ingestive, parenteral and transplacental.

4. Environmental carcinogens according to specific action mechanisms: cancers developing at site of primary contact, cancers developing at sites of selective deposition, cancers developing in organs with special functional or toxic affinity for carcinogens, cancers developing in organs of excretion of carcinogens, cancers developing on the basis of functional abnormalities due to certain dietary deficiencies or allergenic reactivities involving the possible mechanism of indirect carcinogenesis.

5. Environmental carcinogens having specific target organs or tissues: skin, lung, bone, bladder, etc.

Because of the still existing large defects in our knowledge on many aspects of environmental carcinogenesis and on account of the relative newness of most information available on this matter no

country or no subdivision of any country has so far developed a comprehensive program of cancer control by preventive measures, based on any one of the five principles listed. Wherever preventive practices are employed, they cover as a rule only rather narrow segments of the problem as a whole. Preventive measures have been applied more widely to the control of individual occupational cancer hazards than to any other type. But even in this particular field wide variations exist for different countries and even here the scope of preventive controls has remained rather fragmentary so far under the best of circumstances. The principle of preventive control of specific carcinogens (principle 1) has in general been used in the occupational cancer field. Only very recently attempts have been made in some countries to utilize principle 2 (environmental carcinogens according to the general type of exposure) in an attempt to establish comprehensive preventive measures against potential and actual cancer hazards associated with food additives and contaminants and with air, water and soil pollutants of various physicochemical natures.<sup>1,2</sup>

### Methodology of Preventive Measures

Many, although by no means all, of the known environmental cancer hazards originate with specific industrial activities and products and spread subsequently from there to other industrial and commercial establishments and finally to the consumer following the lines and directions of distribution of the particular carcinogenic materials involved. It is for these reasons that specially exposed worker groups sustain the most marked exposures to these agents and consequently develop most often characteristic exposure stigmata as well as cancerous sequelae. A logical and rational approach to the preventive control of many environmental cancer hazards, therefore, may well start at the industrial level. If a complete arrest of the hazard at this point, however, should prove to be impossible or impractical, an extension and adaptation of suitable pre-

ventive measures found useful in industry along the line of spread becomes pertinent for the protection of the general population.

### Prevention of Industrial Cancers

The following measures are indicated or may be considered at an industrial level:

#### A. TECHNOLOGIC ENGINEERING MEASURES

1. Screening of all chemicals, which may be suspected for some theoretical reasons of possessing carcinogenic properties, in experiments on suitable animals for determining their potential carcinogenicity. Unless the continued production and use of a chemical found to be carcinogenic in such tests is essential on economic or biologic grounds, its manufacture should be stopped. Such steps were taken in regard to 2-acetylaminofluorene and styryl-430. All individuals who have contact with such a chemical should remain for several decades under periodic medical supervision for the possible appearance of cancers causally related to the specific exposure sustained previous to the arrest of manufacture.

2. Elimination of a carcinogenic agent, which has produced cancers in man, from the human economy should be obligatory if such an agent can be replaced without serious harm by a noncarcinogenic although perhaps more expensive one. The discontinuation of the production of beta-naphthylamine and of 4-aminodiphenyl by American, English, German and Swiss manufacturers provides an example in point.

3. Whenever the further production and use of a carcinogenic agent becomes unavoidable, measures must be taken either to prevent or to reduce contact with it. One of the most effective technologic measures in this respect is the employment of a closed system, or remote control system of production. Such measures however, may not be equally well applied to the subsequent phases of the handling and use of a carcinogen, i.e., packaging, shipping, processing, using and consuming,

and therefore may provide an only partial control of an occupational cancer hazard.

4. Another and perhaps ultimately more effective method of obviating further cancer hazards under such conditions consists of the conversion of a carcinogenic compound, especially if it is an intermediate, into an equally useful noncarcinogenic one. This approach, for instance, has been used in overcoming cancer hazards related to beta-naphthylamine, by sulfonating first the nitro-compound which then is aminized forming a noncarcinogenic sulfonated naphthylamine. In evaluating the real effectiveness of such measures, consideration should be given to the possibility that a noncarcinogenic conversion product may subsequently be disintegrated in the human body under special conditions with the release of its carcinogenic component.

It is also important for ensuring an effective reduction of a carcinogenic hazard, that carcinogenic chemicals, when present as impurities, be removed from the finished product before their wide distribution is permitted. Such precautions, for instance, apply to alpha-naphthylamine which in its commercial form always contains from 2 to 5 per cent beta-naphthylamine as an impurity. This contaminant should be removed at the factory before alpha-naphthylamine is allowed to enter the usual trade channels. The number of potentially or actually exposed individuals would be reduced greatly by such a precautionary measure. Similar procedures are indicated in freeing the noncarcinogenic diphenylamine from its carcinogenic impurity, 4-aminodiphenyl.

5. Cancer hazards from carcinogenic dusts and fumes or vapors sometimes can be eliminated or greatly reduced either by using a wet system of handling or by transforming water insoluble compounds through salt formation into soluble ones which can be handled technically more safely. The suppression of asbestos dust by wetting procedures reduces exposure, decreasing not only the liability to asbestosis of the lung among exposed workers but also that to cancer of the lung which depends upon the preexistence and co-

existence of asbestosis. However, care must be taken here that the agents used for the wetting process are not carcinogenic by themselves, such as carcinogenic constituents of petroleum derivatives. Wet drilling methods in arsenic and radioactive ore mines reduce exposure to hazardous dusts. The substitution of salts of benzidine for the base reduces to some extent the bladder cancer hazards known to be associated with contacts with both the base and its salts, because of a reduced cutaneous, respiratory and ingestive contact with benzidine salts.

6. Hoods and adequate exhaust ventilation properly placed for an effective removal of carcinogenic dusts, fumes, mists, sprays and vapors may be of distinct benefit in reducing exposures to various carcinogenic chemicals. The protective effects of such devices, however, may be jeopardized, if the contaminated exhaust air is not adequately cleaned by the installation of scrubbers and filters before it is released into the atmosphere. An uncontrolled release of carcinogenic exhausts may create neighborhood cancer hazards for persons living or working in the environs of carcinogenic operations. A considerable spread of carcinogenic material from a restricted area into other parts of a building may also occur if air conditioning equipment serving a carcinogenic operation is connected with that of the rest of the building and the air exhausted from the carcinogenic operation is in part recirculated throughout the entire building, contaminating additional quarters.

7. Storage of carcinogenic raw or waste materials, such as radioactive and arsenical ores and slag, chromate slag, petroleum carbon and coal pitch should be in sheds, old mine shafts or other structures in which these materials are protected against distribution into the neighborhood by the action of winds or from which they may be leached into sources of drinking water supplies by rain. Whenever such measures are impracticable, the slag heaps should be kept wetted down continuously. Neighborhood contamination with carcinogenic materials may also

result from the burning of containers emptied of carcinogenic aromatic amines in yards of chemical and dye establishments. Similarly, the disposal of waste oil of refineries may produce a considerable degree of air pollution with carcinogenic soot. Such practices should be discontinued and prohibited.

Related contaminations of the environmental air and water with carcinogenic industrial waste may occur with the release of arsenic-containing fumes from metal ore smelters, of chromium-containing fumes from chromate manufacturing plants and catalytic cracking towers of refineries, from chromate pigments used for spraying airplanes, of radioactive substances from establishments producing, handling or using radioactive materials, of soot containing aromatic and aliphatic hydrocarbons from refineries, coke ovens, carbon black plants, tar factories, gas plants and power plants. Such pollutions can be kept within reasonable limits by the installation of electrostatic precipitators, sprinkler systems and scrubbers, or by a very high-level discharge of such wastes from smoke stacks or by filtering systems or settling basins.

8. Wherever ionizing radiations are produced or used, adequate shielding devices should be installed not only for the protection of the operators but also for those working or living in adjacent rooms or buildings, particularly when high power equipment is employed, giving rise to high intensity scatter radiation.

9. Proper attention to suitable types of building materials and construction patterns may also assist in diminishing the degree of exposure to certain carcinogenic materials in industrial operations. For instance, it is advisable to use, in the construction of rooms in which carcinogenic aromatic amines are produced or handled, materials for the walls, floors and ceilings which do not absorb these chemicals and retain them as a depot. For this reason asphalt tile, brick and wood are objectionable. The surfaces also should be smooth, so that they can easily be washed and should have as few nooks and ledges on which dust can settle as possible. All

equipment requiring maintenance should be so placed that it is readily accessible for servicing by maintenance and repair personnel. The temperature in such rooms should be kept at a low level for reducing the vapor pressure of such substances and for decreasing the sweating tendencies of workers active in such rooms, because the permeability of the skin for these chemicals is increased when the room temperature is high and the degree of exposure thereby accentuated.

#### B. SANITARY INDUSTRIAL HYGIENIC MEASURES

The effectiveness of the various technologic preventive measures must be supported by suitable sanitary hygienic measures. Such activities should be in the hands of experienced and well-trained sanitary engineers, industrial hygienists and safety officers.

1. Adequate plant housekeeping and maintenance of the highest possible cleanliness in the plant area will eliminate those occupational cancer hazards which exist in dirty operations. Such measures are especially essential in plants handling highly potent carcinogens, such as aromatic amines and radioactive materials, where even relatively minute contaminations may create an effective carcinogenic exposure.

2. All machinery and devices employed in reducing or eliminating exposures, such as hoods, exhaust apparatus, electrostatic precipitators, filters, scrubbers and radiation shields, should frequently and periodically be checked for proper operation.

3. Personnel and equipment assigned to accident control in carcinogenic operations should always be kept on the alert, so as to keep accidental contaminations of plant areas and vicinity by carcinogenic materials at a minimum and to extend adequate protective and prophylactic measures to regular operators and accident control personnel.

4. Periodic checks should be made within and without the plant area, including the entire waste disposal area, for determining the concentration and physiochemical status of carcinogenic materials

handled. Whenever possible automatic monitoring devices and alarm systems should be used. Such measures are essential for assessing the efficacy and adequacy of the control procedures taken to protect personnel within the plant area and to discover unsuspected sources of exposure within and without the plant.

5. Routine supervision should be exercised over the compliance with all precautionary measures and safety rules in carcinogenic operations by operators and maintenance and repair men.

6. Workers exposed to carcinogenic agents should be provided with suitable protective clothing, goggles, respirators, gloves, boots, barrier creams, etc., depending upon conditions and indications. Separate lockers and rooms should be available for work clothes and street clothes. Contaminated work clothes should not be taken home for laundering, since such a procedure might spread the cancer hazard to members of the family of exposed workers or to workers employed in public laundries or persons subsequently using the same laundering equipment in public or commercial establishments. Contaminated clothes should be cleaned in the plant under adequate conditions of safety. Fresh work clothes should be supplied at frequent intervals the length of which depends upon the type of carcinogen and the degree of daily contamination. Workers should have adequate bathing facilities and should be required to take a bath after work before leaving for home. Meals should not be taken within the carcinogenic area but in specially provided rooms after thorough cleaning of hands, nails and face. Food should not be brought into the hazard area. Workers with dirty and careless working habits should not be employed in carcinogenic operations. All workers should be instructed as to the reasons for the precautionary regulations made and concerning any warning symptoms of cancerous reactions. All accidents or undue exposures from leaks, breaks, etc., should be reported promptly and recorded in the employment histories of the men involved.

7. Safety personnel also should su-



pervise the placing and maintenance of proper warning signs of especially dangerous parts in carcinogenic operations where leaks and breaks in pipes, stills, pumps, etc., as well as spillage of carcinogenic materials (packaging, shipping, loading) is most likely to occur.

8. Particular attention must be paid to the use of proper containers in the shipment of carcinogenic goods. The containers must be constructed in such a way that they can be filled and emptied without causing exposures to the workers. They must be highly resistant to breakage and leakage and, if containing radioactive matter, they must be properly shielded. All containers with carcinogenic materials of all types should carry proper warning signs similar to those adopted in the United States for identifying containers of betanaphthylamine.

Containers and wrapping materials used for shipment of carcinogenic agents should be so constructed that they can be disposed of safely and rather simply, but under no circumstances should they be included among the general trash, where such contaminated matter may become a source of additional environmental exposure to persons within and without the plant area.

#### C. MEDICAL MEASURES

Competent medical supervision of all individuals to be employed, or employed in carcinogenic operation, is an essential facet of any program for the prevention of occupational cancers.

1. Cancer prevention can be practiced successfully in the selection or rejection of applicants for hazardous jobs by applying the following considerations at the medical pre-employment examination. From experience, it does not appear wise to place red-haired or blond individuals, or persons with freckled skin which does not tan but which burns upon exposure to sunlight, in positions entailing unavoidable contact with carcinogenic petroleum products, coal tar, pitch, creosote and anthracene oil, or necessitating prolonged and intense exposures to sunlight or ultraviolet radiation because of their high susceptibility to skin cancer. It is likewise not

desirable to employ workers with chronic diseases of the respiratory tract (chronic bronchitis, laryngitis, sinusitis, rhinitis) in operations where they may become exposed to any one of the various respiratory carcinogens, because such individuals are likely to have an impairment of their natural defense mechanisms (ciliary movement and mucus production of mucosal epithelium) and thereby are apt to retain inhaled carcinogenic matter for an unusually long time in direct contact with the epithelial lining, causing an abnormal intensification of exposure. Such individuals are particularly unsuitable for employment where they may sustain in addition to contact with specific carcinogenic agents, an exposure to respiratory irritants, such as acid and alkali fumes and various organic chemicals (aldehydes, etc.). Some consideration in this respect may also be given to the advisability of employing heavy smokers in such operations.

Persons with chronic liver diseases of infectious, chemotoxic or nutritional origin do not seem to be suitable for work where they may have undue contact with carcinogens which are either primary hepatic carcinogens or carcinogens normally metabolized by the liver, such as chlorinated hydrocarbons, aromatic amines, estrogens, azo-dyes and selenium. The presence of abnormalities in the urinary tract which may hinder the free flow and excretion of urine (ureteral and urethral obstructions, prostatic hypertrophy, diverticula and prolapses of the bladder) or which are associated with chronic inflammatory changes of its mucosal lining (infectious, chemical, allergic cystitis) might be considered as sufficient reason for rejecting applicants for employment in operations where urinary carcinogens—aromatic amines: alpha- and beta-naphthylamines, their derivatives (dyes, rubber antioxidants), benzidine, 4-aminodiphenyl, auramines—are produced or handled. It finally may be wise to exclude individuals with chemical allergies of the blood-forming tissue (agranulocytosis, aplastic anemia, purpura, etc.) from contact with leukemogenic agents (benzol and related myelotoxic solvents, ionizing

radiation) and chemicals and drugs eliciting agranulocytic and related blood dyscrasias, because of the possibility of an abnormal tendency of such individuals to develop leukemic reactions. Special care in this respect should be taken in the employment of female workers of a child-bearing age because of the possibility of transplacental transfer of such susceptibilities or of the agent to their offspring, or of transmission in the milk.

Since cancers may be the result of exposures to carcinogenic agents from various sources, a good medical pre-employment history should contain adequate data on any previous occupational and non-occupational exposures to carcinogenic agents so as to estimate the approximate total carcinogenic load an applicant has acquired before entering a hazardous operation and the possible specific cancerogenic liabilities which might be associated with such exposures. The suitability of an applicant for work entailing exposure to a specific carcinogen should be determined on the basis of such data and on the results of a detailed medical examination for the existence of specific exposure stigmata and precancerous reactions related to carcinogenic exposures sustained prior to his application. It would not be desirable for any person with a history of a significant exposure to a carcinogen to accept employment in another carrying the same or a similar hazard.

2. The already available factual medical knowledge on environmental carcinogenesis may also profitably be applied to the application of preventive measures aimed at the maintenance, activation and strengthening of the normal defense mechanism of the body against the action of carcinogens. The preservation of sebum or its replacement when removed through cleaning procedures, by the use of suitable substitutes, such as lanolin, or properly designed barrier creams, would provide some degree of protection against the carcinogenic effect of coal tar and petroleum and shale oils. The use of similar creams or lotions containing chemicals which absorb ultraviolet radiation would be indicated against excessive exposures to solar or

ultraviolet radiations. A similar action may be expected from chemicals which stimulate the production of melanin pigment or cornification of the epidermis, or which protect it against chemicals causing a depigmentation. The administration of sulfhydryl compounds, such as BAL, aids in the detoxication and excretion of arsenicals. Chemicals which mobilize calcium and related chemical bone seekers (radioactive substances) may aid in the removal by excretion in the urine of radioactive matter deposited in the bones (parathyroid hormone, vitamin D, chelates). Studies on chelates forming metal complexes with chromium, nickel and beryllium might lead to means suitable for the demetallization of the body exposed to carcinogenic metals.

Individuals having respiratory contacts to carcinogens should be protected against simultaneous exposures to chemical, allergic or infectious agents which might weaken and damage the normal defense mechanisms of the respiratory tract (nasal cavity, trachea, bronchi). Maintenance of a normal liver and kidney function and protection against any injurious infectious, chemotoxic or nutritional injury deserves serious medical consideration for preserving the normal metabolism and excretion of certain carcinogens.

3. These aspects of medical attention should be complemented by periodic medical examinations of all regular operators as well as of those who work intermittently in carcinogenic operations (maintenance men, repairmen, supervisors, truckers, shippers, etc.) or who may become exposed to carcinogens handled there for reasons of environmental pollution (yardmen, guards, clerks, nurses, executives, etc.). Such studies may include, where indicated, x-ray pictures of the lungs (soot, asbestos, chromium compounds, beryllium, radioactive ores, arsenic, nickel, mustards, isopropyl oil), bones (radioactive materials, beryllium) and nasal sinuses (isopropyl oil, nickel, radioactive materials); cystoscopies (aromatic amines, dyes, rubber antioxidants); laryngoscopies (isopropyl oil, lubricating oils, mustard gas); rhinoscopies (nickel, chromium

compounds, isopropyl oil); tests for the demonstration of or reactions to carcinogenic agents in blood, urine, secretions, excretions and tissues (benzol in bone marrow obtained by sternal biopsy, aromatic amines in urine, asbestos bodies in sputum, and lung tissue, beryllium in sputum, lung tissue, urine and bones, arsenic in urine, hair and nails, chromium in blood and urine, radioactivity in exhaled air, urine and tissues). The examinations should serve also for the demonstration of any significant exposure stigmata and precancerous lesions which may require biopsies and cytologic studies (sputum, urine, nasal secretion). They thus are not only important for the establishment of effective contact with a carcinogenic agent but also essential for assessing adequacy of the protective and preventive measures.

4. Because of the long latent period of occupational cancers, medical supervision of exposed individuals should be continued for 20 to 30 years following cessation of exposure, which may be as short as six months for aromatic amines and asbestos and still result in some exposed persons in cancer formation after a lag period sometimes exceeding one or several decades. It is essential for this reason also that detailed medical records are kept and preserved on all exposed persons over periods of at least five decades and that such medical data are supplemented by corresponding detailed employment data giving information on chemicals contacted, exposure conditions, etc. Only when such information is available can reliable evaluations as to the presence of occupational cancer hazards and the efficacy of preventive measures be made.

6. Because of the usually long latent period of occupational cancers it is advisable for reducing the number of workers who might develop cancer from occupational contacts to employ wherever possible, individuals above forty years of age. Through the adoption of such an employment policy for workers to be engaged in carcinogenic operations, it is likely that the loss of workers from such groups by death from noncancerous occupational causes occurring before the lapse of the

proper latent period would result in a lessening of the number of occupational cancers and would be associated, even when occupational cancers should develop, with a possible death from such causes at an age when the end of the normal life span has been reached or is approaching.

The employment of children and young adults in carcinogenic industrial operations is objectionable on grounds of well known biologic facts concerning the preparatory period of environmental cancers.

Since the effects of exposures to carcinogenic agents and devices generating ionizing radiations are largely irreversible, it is likewise imperative that the number of exposed workers be kept at a minimum and that appropriate steps be taken to avoid any undue labor turnover in such operations.

In view of the fact that evidence obtained in man and experimental animals indicates that carcinogenic chemicals can penetrate the placental barrier and may be excreted with the milk thereby causing a possible exposure of either the fetus or the infant, pregnant women should be excluded from employment in carcinogenic operations. Since some of the carcinogenic chemicals are stored in the tissues of the body from which they are subsequently slowly released, consideration should be given to the adoption of a policy of prohibiting the employment of all women of childbearing age in industrial operations in which such carcinogenic chemicals are produced, handled, processed or used.

#### D. PUBLIC HEALTH MEASURES

The prevention of occupational cancer hazards is of importance to public health agencies for two reasons: 1. They represent significant medical, medicolegal, economic and sociologic disease problems for industrial and professional workers which are amenable to preventive control measures or should be made so. 2. They are the prototypes of environmental cancer hazards involving members of the general population through the spread of the carcinogenic agents into the general human environment mainly in the form of or as parts of consumer goods and industrial wastes,

and therefore become objects of public health interest requiring preventive control. Procedures and regulations which may prove useful in this respect are the following:

1. Registration or licensure of all factories, workshops, laboratories and other establishments producing, handling or using carcinogenic materials of any kind with proper public health agencies is desirable. This would make available essential information concerning the location of carcinogenic operations within a certain jurisdictional district, the types of agents and exposures present, the number, sex, race and age of persons exposed, degree of labor turnover and nature of technologic, sanitary and medical preventive measures observed or required to ensure acceptable and safe labor standards. Such data would provide also a rational basis for determining existence and degree of any environmental pollution with carcinogenic agents which may be associated with the release of industrial wastes into the air, soil and water of the vicinity of the plant or following the routes of distribution of its products.

2. A system of regular surveys or inspections of all plants using, handling or producing carcinogenic materials by public health officials is desirable for checking on and enforcing the observance of any preventive and precautionary measures which might be deemed necessary for the protection of workers and the general public in pursuance with regulations or laws enacted. Specially trained physicians, industrial hygienists and factory inspectors should be entrusted with such tasks.

3. All precancerous and cancerous lesions produced by or suspected to be produced by recognized, probable or potential carcinogens, as well as cancers of all types observed among workers employed or once employed in operations with carcinogenic hazards, should be made notifiable with the appropriate public health agency. All persons having knowledge of these cancers should be held responsible for such reporting by law. Regulations of this nature are essential for ensuring an effective control of occupational

cancers by use of preventive measures.

4. Public health agencies should establish registers of occupational cancers according to types of causal agents, types of cancers produced, types and degrees of exposure, length of exposure, preparatory and lag periods, types of operations involved, types of products concerned, types and number of individuals exposed. When such basic data are at hand, information is available for formulating rational and practical regulations and laws for a control of occupational and related environmental cancers by preventive measures.

5. All available means of education and information should be used by public health agencies for spreading all available knowledge of recognized, probable and potential occupational carcinogens and cancers among all concerned with such matters, including worker organizations, for ensuring an early recognition of actual and possible occupational cancer hazards and for making possible the institution of preventive measures before such hazards may produce an epidemic-like appearance of cancers.

6. Mechanical devices capable of producing carcinogenic actinic energy should carry proper warning labels, and should be furnished with explicit instructions as to suitable protective measures. Carcinogenic chemicals should be packed in strong, leakproof containers to eliminate any danger to loaders, shippers and other persons handling them during transport, storage, merchandising or use. The containers should be constructed in such a way that they can be emptied without hazard to the workers performing the task and to those employed nearby. Such requirements are particularly applicable to highly potent occupational carcinogens, such as beta-naphthylamine and radioactive substances. Carcinogenic material containers should carry prominent labels with appropriate warnings.

If the various preventive measures outlined were effectively applied, it is likely that an appreciable degree of preventive control of numerous occupational cancer hazards might be obtained without causing through the unavoidable adjustments

any serious derangement of present and future industrial activities and their associated financial and economic interests. While the problems related to an introduction and use of preventive measures against nonoccupational environmental

cancer hazards are, in many respects, similar to those associated with the occupational types, they present in some aspects much greater complexity for various reasons and, therefore, are less readily amenable to preventive methods of control.

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## Milk Cartons and Cancer

[Following is an example of a nonoccupational environmental cancer hazard referred to in the last paragraph of the preceding article by Dr. Hueper.]

In *CA*, May-June 1958, page 106, a correspondent inquired concerning the possible carcinogenic nature of the wax used in coating milk cartons. Following publication of this "Doctors' Dilemma" the Director of the Medical Research Division of one of the largest oil companies wrote us that such studies had been in progress for some time. In experiments then under way in two separate laboratories, 24 milk-carton waxes, injected in large quantities (0.5 gm.) subcutaneously into mice, had produced no tumors in 35 weeks, and waxes of milk-carton quality implanted in the bladders of mice had produced no tumors. The petroleum industry was stated to be one of the few industries which had recognized its responsibilities in this direction and taken steps to provide definitive answers.

[Dr. Paul Kotin, University of Southern California, reported to the National Conference on Air Pollution, in Washington, D. C., November 19, 1958, that "protein materials, normally present in blood and in cells, are capable of freeing cancer-producing chemicals from the particles on which they are carried so that biological activity on their part can result."

Hans L. Falk, Paul Kotin and Adele Miller, University of Southern California, in an article, *Milk as an Eluent of Polycyclic Aromatic Hydrocarbons Added to Wax*, in *Nature* 183:1184-1185, April 25, 1959, report that milk, a protein solution, elutes polycyclic hydrocarbons from paraffin waxes despite the hydrophobic nature of the hydrocarbons. Several dairy waxes used commercially to impregnate milk cartons were found to contain the carcinogen, 1,2,5,6-dibenzanthracene, about one part per million. At 20° C. 94 per cent of 3,4-benzpyrene added to dairy wax was eluted by whole milk, 91 per cent by half milk and half cream, 81 per cent by buttermilk and 74 per cent by skimmed milk. These results show the wisdom of the recommendation of our original consultant, Dr. W. C. Hueper, that the oil industries should undertake a comprehensive and competent study of the waxes furnished to the dairy industry. This is but one item in Dr. Hueper's one-man crusade against carcinogens in foods and in industry—a crusade which is beginning to show results in spite of industrial obstruction and official lethargy. Dr. Hueper has been referred to as a devoted and dedicated "man with a cause".—Ed.]



## Case Report

### Cystosarcoma Phyllodes

*Harry M. Nelson, M.D.*

Mrs. S. S., aged 46, white, was admitted to Woman's Hospital on August 18, 1954, because of a growth in the left breast. The patient had noticed a firm, small tumor in the breast during the past twenty years. Four months prior to admission the breast began to enlarge rapidly. It soon became tender, painful and discolored. She visited a "drugless healer" two months before her hospitalization. He gave her "light treatment and massage" three times weekly. Three weeks before entering the hospital the tumor broke down, followed by considerable bleeding, ulceration, exudate and odor. Because of the enormous size of the breast, the patient wore a sling for support, and large pads to absorb the discharge. Gradually she became so weak, because of inanition, bleeding and fever, that she remained confined to her room.

The patient ran a septic type of temperature in the hospital, varying between

101° and 104°. Her hemoglobin was 4.2 Gm./100 ml., RBC 1,150,000 per cu. mm. and WBC 15,250 per cu. mm. on first examination. Antibiotics and six whole-blood transfusions were given in preparation for surgery. The sloughing was extreme and the odor so penetrating that it was necessary to isolate the patient.

The fever persisted until the day of operation. A simple mastectomy was performed on September 1. A wide elliptical transverse incision was used, and the skin closed with a sliding graft. The wound healed rapidly and the patient left the hospital in excellent condition after eight days. At time of discharge she was afebrile, with a hemoglobin of 10.3 Gm./100 ml. and an RBC of 4,020,000. Admission weight was 102 pounds (Fig. 1). Weight October 30, (Fig. 3) was 122 pounds.

*Pathological Considerations.* The tumor weighed approximately 4 Kg. and upon section exuded mucinous material. The skin over the neoplasm was ulcerated and

*Chief Gynecologist, Woman's Hospital, Detroit, Michigan.*



Figure 1

inflamed. Histologic examination revealed the tumor to be composed of stellate-shaped fibrocytic cells that did not vary much in size, shape and staining reaction. The tumor was only moderately cellular and the connective tissue cells were separated by the mucinous stroma. In only a few areas were ductal elements recognized and in these the epithelium appeared entirely mature (Fig. 2).

*Diagnosis.* Cystosarcoma phyllodes, benign.

*Discussion.* Cystosarcoma phyllodes is a term attributed to Johannes Müller who in 1838 first described this tumor. Sarcoma, at that time, apparently meant a "fleshy mass" and not a malignant tumor as currently used. Cystosarcoma phyllodes, unqualified, refers to a benign tumor that nearly always arises from a fibroadenoma, the two differing only by size. Malignant variants do occur in which the stroma resembles a fibrosarcoma but with benign

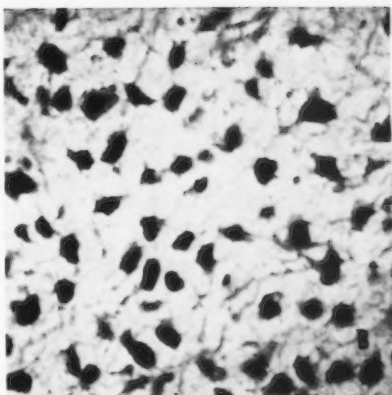


Figure 2

ductal epithelium. Such variants are capable of metastases, especially to the lungs. These giant tumors, benign or malignant, are rare and are really museum curiosities. This particular case was considered as a benign variant and there is no evidence of recurrence four and a half years after operation.

It is difficult to understand in this enlightened medical era how an intelligent patient would allow a growth to reach this size. Our educational program still misses many people.

*Fig. 1. Picture taken day after admission. Note the patient supporting the growth. Pads are covering her hands.*

*Fig. 2. High power magnification of stromal elements showing tumor to be composed of stellate cells separated by myxomatous intracellular material.*

*Fig. 3. One month after operation.*



Figure 3

# Book Services for the Physician

Mary Louise Marshall

In the advance and expansion of medical knowledge in this twentieth century, the means by which the physician may keep himself informed become increasingly important. Scientifically speaking, to stand still is to fall behind. In spite of television and recorded sound, the printed page is still the best instrument for the communication of knowledge, valuable as other adjuncts may be. However, in the mass of medical literature appearing in books and journals today the doctor is faced with the problem of what journals and books to read and how to get them. No one can hope to own even a considerable portion of the current publications devoted to a single specialty. How then can he learn of additional contributions in other fields or from other countries, and how and by what means can he secure access to the publications he needs?

Although nothing can take the place of a personal library, one solution to the problem is the cooperation of groups in a hospital or society in the pooling of resources to form a library. Where the facilities of a medical school library are available, the problem is not so acute, but such organized medical libraries are few in non-urban areas. This urgent need for medical books and journals is felt especially by young physicians who have had use of medical libraries throughout their years of professional training, then go to smaller communities to begin practice, without large libraries of their own and without sufficient income for extensive book purchases.

## Abstract Journals

There are several ways for the medical man so situated to secure help in his need for current medical information. First should be mentioned the use of abstracts.

Although such short reviews can never take the place of the original article, they do valuable service in acquainting the reader with what is new in all fields of medicine and in supplying a reference in case the complete article is needed. Many specialty journals publish abstracts of publications in their own field. A notable example of this is the excellent *International Abstracts of Surgery* published in conjunction with *Surgery, Gynecology & Obstetrics*. Abstracts are here classified by organ and by body system; a detailed table of contents in each issue and a volume index make the abstracts readily available.

Some journal publications are devoted entirely to abstracts and certain of these are of special interest to readers of *CA*. In the series of abstract publications issued under the title *Excerpta Medica*, Section XVI, is devoted to cancer\* in all its aspects. Its twelve monthly issues in 1957 contained 4,687 signed abstracts in English of articles in many languages and originating in many countries. Author and subject indexes make this an especially valuable reference tool. A more specialized publication is *Leukemia Abstracts* sponsored and distributed gratis by the Lenore Schwartz Leukemia Research Foundation.† Abstracts are grouped by phase of the subject treated, as Case Reports, Diagnosis, Etiology, etc., and coverage includes many English abstracts of articles originally published in other languages. Here also the abstracts are useful not only for themselves, but also in furnishing the references to the complete articles.

Other important abstract journals published in English are *Biological Abstracts*, *Chemical Abstracts*, *Abstracts of World Medicine*, *Bulletin of Hygiene*, *Helminthological Abstracts*, *Multiple Sclerosis Abstracts*, *Nuclear Science Abstracts*, *Ophthalmic Literature*, *Physics in Biology*

<sup>\*</sup>Rudolph Matas Medical Library, Tulane University of Louisiana, School of Medicine, 1430 Tulane Avenue, New Orleans 12, La.

<sup>\*</sup>Excerpta Medica Foundation, 2 East 103rd Street, New York.

<sup>†</sup>Leukemia Abstracts, John Crerar Library, 86 East Randolph Street, Chicago.

and Medicine, Review of Applied Entomology (Series B), Review of Medical and Veterinary Mycology, Tropical Disease Bulletin, Tuberculosis Index and Abstracts, Water Pollution Abstracts, and the various sectional publications of *Excerpta Medica* (Anatomy, Anthropology and Histology; Cardiovascular Diseases; Cancer; Chest Diseases; Dermatology and Venereology; Endocrinology; General Pathology and Pathological Anatomy; Geriatrics; Internal Medicine; Medical Microbiology and Hygiene; Neurology and Psychiatry; Obstetrics and Gynecology; Ophthalmology; Oto-Rhino-Laryngology; Pediatrics, Physiology, Biochemistry and Pharmacology; Public Health, Social Medicine and Hygiene; Radiology; Rehabilitation; Surgery). Subscription may be entered for any section of *Excerpta Medica* separately.

In view of recent special interest in Russian science, attention should be called to the recent publication sponsored by our own Public Health Service, *Abstracts of Soviet Medicine*, issued in two sections, Basic Medical Science and Clinical Medicine. This abstract series offers to the English-speaking medical world the first extensive access to current Russian medical contributions.

### Loan Services

Valuable as abstracts may be, they cannot fill the place of the original article and there are several agencies and means by which physicians, who do not have access to organized medical libraries, may obtain a needed article. Certain state agencies maintain libraries and lend material to their patrons. Tax-supported state libraries often lend to physicians in their area, as in the case of State University Medical School Libraries. Iowa and New York are unique in supporting and maintaining State Medical Libraries independent of medical schools.

The Texas State Medical Association maintains a library in its headquarters in Austin and reference and loan services are extended to the Association's members. The library, originally a reprint library,

now has extended its facilities to include extensive journal files, texts and monographs. A collection of medical movies and tape recordings of medical addresses is a valuable adjunct to the library's service to the physicians of Texas. In addition when the library service of the American College of Surgeons was discontinued in 1957, its extensive collection of reprints was turned over to the Library of the Texas State Medical Association with the understanding that reference and loan service to Fellows of the College would be continued from Austin.

The Library of the American Medical Association lends to members single unbound issues of some 1,600 journals received in the office of the *Quarterly Cumulative Index Medicus*. Files for about ten years past are held in the Library for loan to physicians. The collection is further augmented by reprints and tear sheets from duplicate journals. A service charge of twelve cents plus postage is made for each issue borrowed. A specific number of a journal may be requested or the doctor may ask for material on a given subject. In the latter case a parcel or "package library" is made up of unbound issues, tear sheets and reprints on the subject named. The physician borrower pays postage both to and from Chicago.

Certain organized medical libraries have established out-of-town memberships in the library whereby for an annual fee book facilities are available. Such a plan is used in the Orleans Parish Medical Society Library which is administered jointly with the Rudolph Matas Medical Library of Tulane University. In such an arrangement, the library not only may lend its own books but stands sponsor for loans from other libraries borrowed for the physician's use. This is necessary since libraries ordinarily do not lend books out-of-town to individuals except under an arrangement such as that described.

A variation of the privilege of loan used in many libraries in more recent years is the duplication of the article needed by some photographic process. The earliest of these processes was the photostat with which almost everyone is familiar. Then

reproduction of the printed page on microfilm was developed and is widely used. Microfilm has the disadvantage that it must be used with some sort of device for magnification and cannot be read with the naked eye. Some libraries prepare "photo-prints" which are blown-up prints from a microfilm. Within the past few years, various models of "book-copiers" have been developed and are used increasingly. The latter, electrically operated, reproduce facsimile copy which may be prepared and developed automatically. Responsibility for photoduplication is assumed by the one for whom the copy is made and a fee to cover cost of reproduction is charged by the library. Photographic reproduction is used only for uncopyrighted material and for single articles in journals, since even this duplication of copyrighted material is technically an infringement of the law, but thus far publishers have been generous when the single copy prepared is for scientific use.

Currently some libraries are using photocopies instead of out-of-town loans since this makes it possible to retain books in their own collections, saves the volumes the trauma due to transportation, at the same time the borrower is saved the annoyance of the book's return and may retain the photocopy in his own files. This policy has been adopted by the National

Library of Medicine which furnishes a photocopy without cost, in place of a loan, when the request is made through a local library with the indication that the book is otherwise unavailable.

Another recent development of audio-rather than photoduplication designed to help the physician keep abreast with current medical information is *Audio-Digest*, sponsored and produced by the California State Medical Association. This service by means of a tape recorder reports recent advances in General Practice, in Obstetrics and Gynecology and in Surgery. It is used with the customary "play-back." Subscriptions may be entered for any of the three series and recordings are issued monthly.

It is evident, therefore, that through modern developments and services even to physicians in isolated areas and without modern library facilities, current medical information is available if one knows where and how to secure it. The writer will be glad to furnish further details as to any of the services described in response to further inquiry.

"It is chiefly through their books that we enjoy intercourse with superior minds, and these invaluable means are in the reach of all."

—William Ellery Channing

### **Annual Cancer Symposium**

The yearly scientific session of the American Cancer Society will be held October 26 and 27, 1959 at the Biltmore Hotel, New York City. The theme of this year's symposium will be "Evaluation of Early Diagnosis of Cancer." All physicians, medical students and others interested are invited. The complete program will be published in the July-August issue of *CA*.

The American Academy of General Practice will give credit for twelve hours in Category II to those members of the Academy who attend the scientific session.



## Letters to the Editor

From: Marion B. Sulzberger, M.D.,  
New York City.

In the September-October, 1958, issue of *CA*, the article *Radiation Is a Carcinogenic Agent* by C. Lenore Simpson, D.M., states:

The reported surveys which claim no danger from "properly applied" radiation in the hands of dermatologists are inadequate because of the very low percentage of patients followed, the short follow-up period in relation to the long latent period of the disease and failure to define exactly the selection of treated and control cases.<sup>1, 29</sup>

1. Baer, R. L.; Borota, A., and Sulzberger, M. B.: *Late therapeutic results produced by low voltage roentgen rays and other forms of therapy in certain benign chronic skin diseases. J. Invest. Dermat.* 19:325-332, 1952.

29. Sulzberger, M. B.; Baer, R. L., and Borota, A.: *Do roentgen-ray treatments as given by skin specialists produce cancers or other sequelae? Follow-up study of dermatologic patients treated with low-voltage roentgen-rays. A. M. A. Arch. Dermat. & Syph.* 65:639-649; disc. 649-655, 1952.

Careful reading of the two quoted articles will show that the cases studied represented patients with assorted dermatoses who had been treated from five to 23 years previously by superficial radiation, such as given therapeutically by dermatologists when indicated. All patients were brought in for examination in randomized fashion, and the controls who were examined were drawn from the same groups of patients with dermatoses not treated by x rays and examined in the same randomized fashion. Moreover, a small group of the patients who could not be brought in for examinations were visited in their homes, and an equal number of patients treated by other means excluding irradiation, were also visited in their homes. In this manner it was found that those who did not come in for examination failed to do so for precisely the same reasons in the group treated by radiation as in the group treated by other measures. It is therefore to be

inferred that the x-ray treatment was not a factor in preventing patients to return for re-examination. In view of these facts it appears that the implication of Simpson's criticism regarding a "very low percentage of patients followed" is unwarranted.

The fact that the patients were re-examined from five to 23 years after they received their last superficial x-ray treatment seems adequate to refute the statement concerning "the short follow-up period in relation to the long latent period of the disease."

The article refers to "failure to define exactly the selection of treated and control cases." The selection of the treated and control groups is exactly defined in our two articles, namely both the x-ray treated and the control patient groups are described as patients suffering from various superficial dermatoses who came for treatment during the last thirty years to the New York Skin and Cancer Unit in New York City, and the diagnostic groups are precisely specified.

There can be little doubt that this is the largest series of well-followed cases carefully re-examined for evidence of x-ray sequelae at periods of from five to 23 years after they received their superficial x-ray therapy for dermatoses. At present more than 5000 irradiated sites have been examined in this manner. There is, to my knowledge, no parallel to this sort of follow-up in any group of patients treated by x rays for diseases other than those of the skin; and no such adequate follow-up exists of patients and sites re-examined after diagnostic radiation procedures.

The article by Dr. Simpson is, I believe, misleading since it implies in many places as well as in the photographs shown, that radiation damage is more frequent in patients receiving modern radiation therapy from dermatologists than in other groups. All the available evidence shows that today this is not the case. I heartily agree with the author, and have always stated, that radiation therapy for any condition and of any organ should

never be given unnecessarily, never be given in a dosage or quality except that which is strictly indicated for the given condition, never be given except by those fully trained and experienced with the use of the modality for the particular organ, particular lesion and for the specific purposes intended.

Careful reading of our two quoted articles and of the published discussions which followed would indicate that trained and competent dermatologists using standard methods of roentgen therapy in treating superficial dermatoses do not today produce any of the types of skin damage shown in Dr. Simpson's article. Many of her cases, indeed, must have been very old ones or have been caused by negligence, error or by radiation given by those not specially trained in the treatment of the skin.

To condemn a modality which can produce so much benefit and reduce so much human suffering and disability on such evidence, would be like condemning the automobile because of accidents caused by incompetent or drunken drivers.

From: Dr. C. Lenore Simpson, Buffalo, New York.

I would like to make the following comments on the points Dr. Sulzberger raises in his letter.

Almost half of the 1000 patients reported in his articles have received x-ray therapy less than eight years previously. Only 26 had been treated more than fifteen years prior to reexamination. Figures for the 1000 control patients analyzed are not given. This is a short follow-up period for radiation-induced neoplasms, except possibly for leukemia.

There is no evidence in this article that the patients were brought in for examination "in randomized fashion." Rather the

article suggests that they were self-selected by their willingness to attend out of an original group of over 18,000 patients to whom letters were sent. This is a low percentage of follow-up even when the 658 other replies received, indicating that patients were dead or unwilling to attend, are included. Over 200 patients known to be dead are not included in the analysis and no details of the cause of death are given.

It is not stated in the article whether the 20,000 records examined represented all the patients with the diagnoses given who received any sort of treatment at the hospital, nor how the 18,050 to whom letters were sent were selected from those 20,000. There were 450 home visits made, of which 335 were to treated patients, and 115 to control patients. It is not stated how these patients were selected out of the thousands who did not reply to the original letter. Further, the possible reasons for originally selecting radiation or other treatment are not discussed in the article. In any study where the cases are not allotted at random to the treatment groups, a bias is inevitable.


Dr. Sulzberger states that my article implies that radiation damage is more frequent in patients receiving modern therapy from dermatologists than from other groups; in fact, I stated that there is no clear evidence on this point. Photographs were limited by the material available and I have to thank those who kindly provided the illustrations to this article.

That small doses of x rays without subsequent changes in the skin can result in carcinoma of underlying origin has been shown in recent work on carcinoma of the thyroid. Thus I feel that a study confined to the dermatological sequelae, as were those referred to by Dr. Sulzberger, cannot be entirely satisfactory.

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#### **Correction:**

CA 9:60 (March-April) 1959, Column 2, line 5: Read *chance* for *change*.



# new developments in cancer

## **What's in Cigarettes . . .**

Do cigarettes contain carcinogens? Can carcinogens be detected? Here's what was reported in abstracts at the Seventh International Cancer Congress in London:

M. J. Lyons and J. B. Spence (Glasgow, Scotland): Using the reaction of cigarette smoke solutions with the stable free radical *a*  $\alpha$ -diphenyl- $\beta$ -picryl hydrazyl (DPPH) as indicator, free radicals and other reactive materials diminished in reactivity on exposure to light, under oxygen or nitrogen atmospheres. Some reactive compounds, initially present in smoke, may be lost under present methods of bioassay.

A. I. Kosak and P. D. Rosen (New York): Smoke condensate, from which alkaloids and water-soluble compounds had been removed, yielded terpenes, phenols, alcohols, acyclic alkanes and carbonyl compounds.

S. Neukomm and J. Bonnet (Lausanne): One aliphatic and five of the 25 aromatic hydrocarbons isolated induced animal cancers. A number of polymerized and brown-colored substances also isolated accelerated the appearance of spontaneous tumors in laboratory animals.

C. and R. Leuchtenberger and W. Zebun (Cleveland): Mice exposed to cigarette smoke develop a bronchitis associated with proliferative changes of the epithelium.

E. V. Cowdry, V. Suntzeff and G. Ide (St. Louis): Autopsy studies show that the occurrence of pneumonia leads to epithelial patterns similar to those found in heavy smokers.

P. R. Peacock (Glasgow): No primary bronchogenic tumors so far have been found in fowls, pigeons, rats, hamsters and rabbits made to "smoke." One seventh of the rats developed a small wart on the mouth where a cigarette holder was applied. Respiratory tract lesions were observed in fowls smoking two or more years.

R. H. Holland and others (Dallas): Although arsenic is the only constituent of cigarette smoke known to be carcinogenic to man, relatively little importance has been attached to its presence. The arsenic content of cigarettes has increased 300 to 500 per cent in the last 25 years. The concentration of arsenic in cigarettes is much higher than that permitted by law in foods. Filters remove relatively little arsenic.

## **Anticancer Material in Bacteria . . .**

F. Pentimalli (Rome) has reported that whatever it is that stains Gram-positive bacteria destroys tumors. He observed that saprophytic bacteria, *Micrococcus lysodeicticus*, selectively destroyed a number of transplanted and induced cancers without damage to normal tissues. He found that many of the bacteria recovered

from the tumors had lost their stain and concluded that the stain might have been expended in tumor lysis. He has extracted the staining material, possibly a nucleoprotein, and injected it intratumorally and intravenously into tumor-bearing hosts. In every case it led to massive tumor necrosis followed by liquefaction of the neoplastic tissue. The treatment is being tested on human tumors.

#### **Leukemia "Cure" . . .**

Miami investigators have reported that several common agents occasionally cure leukemia IRC/741 in the Fischer line 344 rat, which rarely regresses spontaneously. The agents—as reported by R. Jones, Jr., D. McKenzie, M. Stevens, W. Dunning and M. R. Curtis—are thio-TEPA, chlorambucil, aminopterin, amethopterin and 6-mercaptopurine. The disease also responds to myleran, benzimidazole mustard, the antimalarial mustards, CB 1414 and urethane. Mitomycin C is highly active.

#### **Isolation and Perfusion . . .**

Two or three years ago, investigators at Tulane University School of Medicine began testing a new technique on cancers which had metastasized but still were confined to areas served by certain arterial systems. They isolated the involved areas, passed its blood supply through a heart-lung machine and loaded this separate circulation with nitrogen mustard. The highly concentrated drug carried a mighty wallop. But side effects were minimal because it was confined to the shunted circulation and did not enter the system. In some cases tumors rapidly withered away. Now University of Minnesota investigators have applied the procedure to metastatic tumors, which appear confined to the head and neck region. Of 15 patients treated in this manner, two eventually became clinically free of cancer, seven others showed substantial diminution in tumor size, and in all patients, pain vanished. The best responses were obtained in patients who had not been irradiated previously.

The results are based on very short term observations, however. At last report, the longest elapsed time since treatment for any patient was seven months. The Minnesota investigators are Doctors J. Bradley Aust, Robert Ausman, Ward Griffen and Bernard Zimmerman.

#### **Radiation Cancers . . .**

That total body or localized radiation increases the cancer incidence among rats, reported by J. and H. Maisin, P. Maldague and A. Dunjic (Louvain). The cancers are of all histological types. Animals irradiated on the abdomen have about six times the normal incidence of cancers. The cancers are long latent, sometimes appearing late in the normal lifespan of the animals.

#### **Pigment Cell Hormone . . .**

A group of scientists working with Dr. Klaus Hofmann, Professor of Biochemistry at the University of Pittsburgh School of Medicine, have synthesized the entire amino acid sequence of melanocyte stimulating hormone (MSH). The achievement represents a major step in the precise analysis of the large molecule protein hormones of the pituitary; and it opens the door to rational investigation of several diseases involving pigment aberrations—possibly including melanoma. The Pittsburgh group found amino acids present in the MSH molecule and determined the proportions of nine of them. Their first synthetic product was potent. But its strength was increased 25-fold and its recovery rose to 93 per cent of theory in the form of a carbobenzyloxy derivative.

#### **Mongolism and Leukemia . . .**

Several investigators have discovered independently the simultaneous existence of mongolism and leukemia in children under four years old. Drs. William Krivit and Robert A. Good of the University of Minnesota have found these observations intriguing and have appealed to investigators and medical centers for reports on similar

occurrences. The scientists estimate that in the normal course of events, there would be a maximum of 12 children in the United States every four years having both diseases. Their preliminary findings indicate at least 34 such cases over a four-year period (1952-1955); and they have found that physicians seldom report these cases. "The data seem to establish that a common factor is operating to result in

the occurrence of leukemia in mongoloid children in a frequency far in excess of its occurrence in the general population," the scientists have reported. "A positive prospective demonstration that the simultaneous occurrence of these two rare diseases is more than circumstantial might be most important in the ultimate understanding of the nature of either or both diseases."

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### Second Workshop Conference on Lung Cancer Research

A two and a half day conference on lung cancer research was held at Arden House, Harriman, New York, on February 27, 28 and March 1 under the sponsorship of the American Cancer Society. The conference was the second workshop conference of this type. The first conference—on the fundamental aspects of the disease—was held at the Cavalier, Virginia Beach, Virginia, November 7 and 8, 1957. In attendance were some 80 participants including six who came from abroad for the meeting. They were:

John R. Bignall  
Institute of Cancer Research  
Royal Marsden Hospital  
London, England

William Nicholson  
Thoracic Surgery, Royal Infirmary  
Manchester, England

J. G. Scadding  
Dean and Director of Studies  
Institute of Diseases of the Chest  
London, England

R. Passey  
Chester Beatty Research Institute  
Institute for Cancer Research  
Royal Cancer Hospital  
London, England

Jean-Louis Cuzin  
Service des Laboratoires, S. E. I. T. A.  
Paris, France

Hanns J. Bauer  
Medicinalstyrelsens Skarmbildscentral  
Stockholm, Sweden

The conference was arranged so that a full day of major addresses was followed by a full day of workshop sessions. On the morning of the third day participants assigned to report for each workshop presented summary statements of the previous days' discussions.

Three innovations were tried out in planning the conference and proved to be highly successful. In addition to experts in the clinical specialty of each workshop, one representative from each other specialty was assigned to represent his own specialty in each workshop. For example, the workshop on Surgery, in addition to eleven surgeons had one pathologist, one radiologist and one internist assigned to represent their respective fraternities.

A second innovation was that a biometrician or statistician was assigned to join each workshop and act as the "statistical conscience" of the group.

Thirdly, each participant was given a topic on which to introduce the discussion. The group was asked to try to draw a line between satisfactorily established facts and concepts requiring further research. Out of the latter each workshop was to identify those projects which, in its opinion, were most urgently needed. The statistician was asked to help outline the design for such studies.



Some indication of the success of the conference is reflected in the fact that several projects arising from the workshop sessions are now underway and others are being submitted to the Society as applications for grants. The enthusiasm of the participants was well expressed in letters received since the meeting: "The meeting was an excellent one—unbeatable—" "I enjoyed the workshop experience tremendously—" "I wish to express my enthusiastic opinion concerning the outstanding excellence of the recently concluded workshop on lung cancer research at Arden House—Truly, the workshop represents another 'milestone' of progress in our attack on lung cancer—"

The agenda and names of leaders, reporters and statisticians follow:

## JOINT SESSION

### A. NATURAL HISTORY OF THE LUNG CANCER

High-risk groups and lung cancer . . . . .	A. M. Lilienfeld
Cellular evolution of the lung cancers . . . . .	Averill Liebow
Radiologic history of the lung cancers . . . . .	Leo G. Rigler
Association of lung cancer with other pathologic states . . . . .	Max Michael
Profiles of regional and distant extension of lung cancers . . . . .	Alton Ochsner

### B. EARLY DIAGNOSIS AND PREVENTION

Analysis of reports of improved survival . . . . .	Lester Breslow
The case of lung cancer screening programs . . . . .	Lewis W. Guiss
Prompt identification of solitary pulmonary nodules . . . . .	L. Henry Garland
Methods of inducing sputum production in non-coughing subject . . . . .	Alvan Barach
Some research problems regarding lung cancer control . . . . .	Michael B. Shimkin (absent)
	Ernest L. Wynder and Daniel Horn
Psychologic research and lung cancer . . . . .	George Saslow

Workshop I: Leader, Dr. Alton Ochsner, Ochsner Clinic, New Orleans, Louisiana; Reporter, Dr. John Steele, V. A. Hospital, San Fernando, California; Statistician, Dr. Sidney Cutler, National Cancer Institute, Bethesda, Maryland.

Workshop II: Leader, Dr. Fred J. Hodges, University of Michigan, Ann Arbor, Michigan; Reporter, Dr. J. J. Nickson, Sloan-Kettering Institute for Cancer Research, New York, New York; Statistician, Dr. Carl Zippin, University of California, San Francisco, California.

Workshop III: Leader, Dr. Max Michael, Duval Medical Center, Jacksonville, Florida; Reporter, Dr. Harold Lyons, State University of New York, Brooklyn, New York; Statistician, Dr. Paul Meier, University of Chicago, Chicago, Illinois.

Workshop IV: Leader, Dr. David A. Wood, University of California, San Francisco, California; Reporter, Dr. Marvin Kuschner, Bellevue Medical Center, New York, New York; Statistician, Dr. E. Cuyler Hammond, American Cancer Society, Inc., New York, New York.

Workshop V: Leader, Dr. Abraham M. Lilienfeld, Johns Hopkins University, Baltimore, Maryland; Reporter, Dr. Lewis W. Guiss, University of Southern California, Los Angeles, California; Statistician, Dr. D. Wilner, Johns Hopkins University, Baltimore, Maryland.

A condensation of the Proceedings of this conference has been submitted to a medical journal with wide distribution for early publication.

is higher among white persons, possibly due to more undiagnosed cases among the nonwhite. Of cancers of accessible sites, 62 per cent are diagnosed before spread; of inaccessible sites, 38 per cent. The ten cities surveyed in this epidemiologic cancer study were Atlanta, Birmingham, Dallas, New Orleans, San Francisco, Denver, Chicago, Detroit, Philadelphia and Pittsburgh.

Stein and coadjutors (U. of Chicago) demonstrated great increase in radiosensitivity in animals in which a hyperthyroid state had been induced by administration of thyroid hormones. Extending this finding to the clinic, two lung cancer patients, during a course of radiotherapy, were given orally 400 to 600 micrograms of triiodothyronine daily, raising the basal metabolic rate more than 40 per cent. With a dose level of radiation one third of that conventionally required for such a response there was definite regression of the tumor. Radiation was discontinued at half the customary total dose level because the tumor masses had disappeared. This thyroid synergism, unfortunately, also supersensitizes the overlying skin tissue producing exceptionally early and severe radiation response.

Virginia Gilmore, now Mrs. Yul Brynner (Hollywood Mt. Sinai Hospital) is at present working on medical microscopic photography. A year ago she completed a course in cytology equivalent to the training sponsored by many Divisions of the American Cancer Society.

The January 1959 number of Cancer Chemotherapy Reports, issued by Cancer Chemotherapy National Service Center, outlines a cooperative study, probably the most ambitious ever conceived and executed. Into 100 pages is condensed a program of cancer chemotherapeutic research involving a host of research teams in all the medical and paramedical sciences, clinicians, laboratories, clinics and hospitals throughout the United States. Methods of screening the thousands of possible anticancer drugs and of recording the results of their clinical tests are presented in detail. It is to chemotherapy that most oncologists look for greatest advance in cancer control.

Harrington (ACS Crusade Chairman) recently presented some startling economic facts concerning cancer. Lost wages due to cancer amount to \$175,000,000 a year in the United States. The total medical bill for cancer in employed persons is more than \$100,000,000 a year. Business and industry lose nearly 50,000 man-years annually due to

cancer disability. The average cancer hospital patient's medical bill is \$1025. Expenses of home care, follow-up treatment and subsequent medical care are additional. The annual hospital bill for cancer is \$300,000,000 -- 10 times last year's contributions to ACS.

Novikoff (Yeshiva U.) produced resistance in rats to transplanted butter yellow hepatoma by vaccination with the microsome fraction of cancer cells. Seven of eight rats inoculated with this live hepatoma 14 weeks after injection of microsome fraction were completely protected, and six of ten rats were protected by injection four weeks before inoculation with live tumor. All unvaccinated controls died of cancer. Submicroscopic canals inside the cancer cells, are reported to be visible with the electron microscope. These may have significance in explaining high volume ratio of nucleus to cytoplasm in the cancer cell.

Eversole (U. of New Mexico) and DaVanzo (Princeton U.) prevented development of liver cancer in adrenalectomized rats by injecting desoxycorticosterone trimethylacetate (DCT). Butter yellow given to intact rats, whether given DCT or not, produced liver cancer after four or five months. DCT given in small doses to adrenalectomized rats retarded but did not prevent the development of cancer. These rats developed new adrenals from accessory remnants of adrenal tissue. Large doses of DCT suppressed development of the accessory adrenals and small doses permitted them to develop and produce hormones upon which the cancer is dependent.

Graham and associates (Roswell Park Memorial Institute, Buffalo) studied the records of 30,000 patients from the social, economic, physical and emotional standpoints. Cancer of the stomach was found to be commonest among middle and lower socioeconomic groups, people with unhealthy teeth and gums, heavy drinkers and those who take very hot foods and drinks. Cancer of the uterine cervix was most frequent in women who marry early in life, have many children early, have menstrual pains, tensions and nervousness and have been divorced, widowed or recently bereaved. Lung cancer was commonest among men who smoke many cigarettes and smoke them short. Breast cancer was most frequent in women who are single or who marry and have no or few children and do not nurse them. Leukemia had a high incidence in individuals whose mothers had been irradiated while pregnant and in those with allergies and infection.

# COMING MEDICAL MEETINGS

<b>Date 1959</b>	<b>Meeting</b>	<b>City</b>
May 18-20	Radiation Research Society	Pittsburgh
May 19-21	Massachusetts Medical Society	Boston
May 21-23	American Association for the History of Medicine	Cleveland
May 24-29	National Conference on Social Welfare	San Francisco
May 25-27	American Gynecological Society	Hot Springs, Va.
May 25-27	American Trudeau Society	Chicago
May 26-29	American College of Cardiology	Philadelphia
May 28-30	American Ophthalmological Society	Hot Springs, Va.
June 1-4	American Dermatological Association	Atlantic City
June 3-7	American College of Chest Physicians	Atlantic City
June 4-5	American Geriatrics Society	Atlantic City
June 4-6	The Endocrine Society	Atlantic City
June 4-7	American Medical Women's Association	Atlantic City
June 4-7	American Therapeutic Society	Atlantic City
June 5-6	American Gastroenterological Association	Atlantic City
June 5-7	American College of Angiology, World Conference on Angiology	Atlantic City
June 6-7	Society for Investigative Dermatology	Atlantic City
June 8-12	American Medical Association	Atlantic City
June 9-11	Canadian Federation of Biological Societies	Toronto
June 15-17	The American Neurological Association	Atlantic City
June 15-18	American Proctologic Society	Atlantic City
June 15-19	Medical Library Association	Toronto
June 18-20	Society of Nuclear Medicine	Chicago
June 26-28	Intermountain Pediatric Society	Sun Valley
June 29-July 3	Irish Medical Association	Killarney
July 4-9	American Society of X-ray Technicians	Denver
July 13-17	International Congress of Radiology	Munich
July 16-17	Oregon Cancer Conference	Portland
July 18-24	British Medical Association Canadian Medical Association	Edinburgh
July 19-25	International Congress of Pediatrics	Montreal
July 22-23	Rocky Mountain Cancer Conference	Denver
July 23-30	International Congress of Radiology	Munich
Aug. 4-9	International Congress of Microbiology	Stockholm
Aug. 9-15	International Congress of Physiological Sciences	Buenos Aires
Aug. 10-13	National Medical Association	Detroit

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